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Insights in neurocognitive aging and behavior: 2021

Edited by
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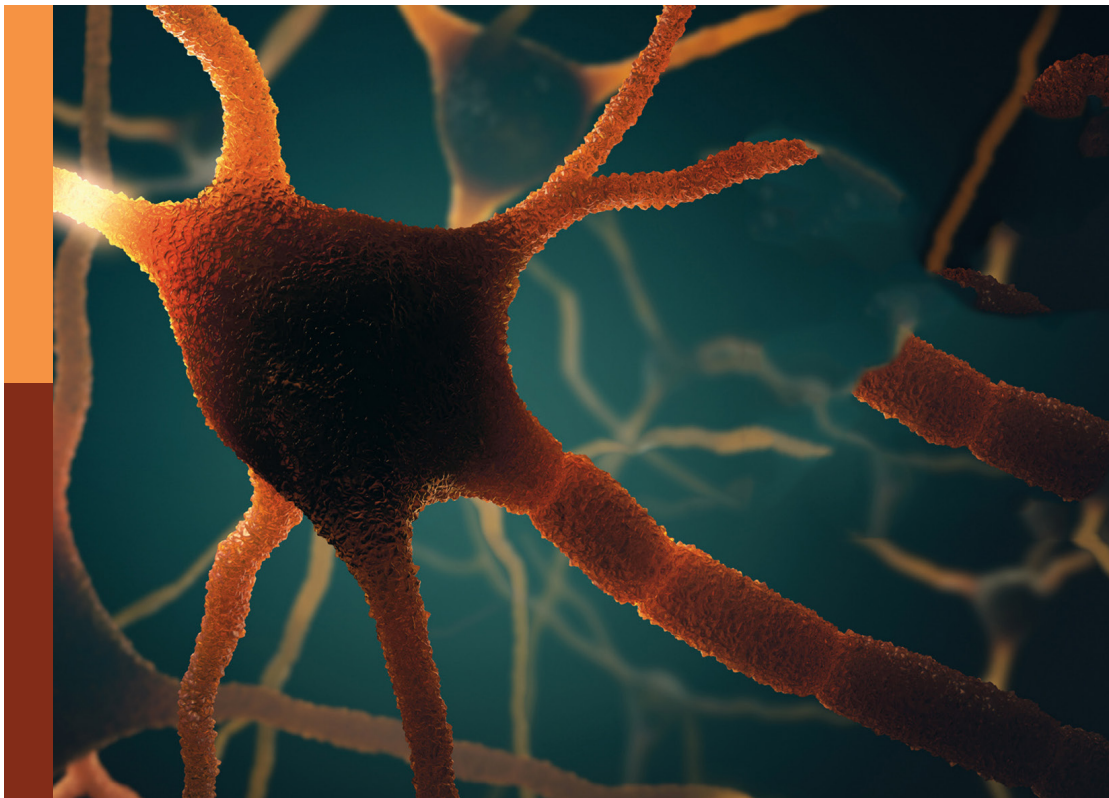
Published in
Frontiers in Aging Neuroscience



ISSN 1664-8714
ISBN 978-2-83251-720-8
DOI 10.3389/978-2-83251-720-8

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Insights in neurocognitive aging and behavior: 2021

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Citation

Nielson, K. A., McDonough, I. M., Soldan, A., eds. (2023). *Insights in neurocognitive aging and behavior: 2021*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-83251-720-8

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frontiers | Frontiers in Aging Neuroscience

TYPE Editorial
PUBLISHED 07 February 2023
DOI 10.3389/fnagi.2023.1147618

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 19 January 2023
ACCEPTED 25 January 2023
PUBLISHED 07 February 2023

CITATION
Nielson KA, McDonough IM and Soldan A (2023) Editorial: Insights in neurocognitive aging and behavior: 2021. *Front. Aging Neurosci.* 15:1147618. doi: 10.3389/fnagi.2023.1147618

Editorial: Insights in neurocognitive aging and behavior: 2021

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KEYWORDS

brain aging, Alzheimer's disease, neuroimaging, biomarkers, cognitive reserve, cognitive aging theories, lifestyle activities, exercise

Editorial on the Research Topic
Insights in neurocognitive aging and behavior: 2021

In recent years, exceptional scientific achievements have led to major advancements in the fast-growing field of neurocognitive aging and behavior. In this inaugural collection, *Insights in Neurocognitive Aging and Behavior: 2021*, we sought to highlight the latest advancements and challenges for the current state of knowledge and future directions in aging neuroscience in the neurocognitive arena. Here we outline the contributions and implications for future research of the 15 papers in this topic collection across four important research areas: (1) novel approaches to identifying and tracking brain aging and impending cognitive decline; (2) neurocognitive markers of risks for Alzheimer's disease (AD) and its progression; (3) lifestyle contributions to cognitive aging and AD; and (4) the status and future of neurocognitive and brain aging theory.

Insights in novel indices of neurocognitive aging

Thirty years of advances in neuroimaging that allow us to visualize brain structure and function *in vivo* have transformed how we think about the aging brain (Risacher and Saykin, 2019). This topic collection addresses this, but also several newer approaches that have promise to further revolutionize our understanding of the aging brain. Huang et al. examined the cognitive implications of carotid artery stenosis (CAS) and associated leukoaraiosis in middle to older age, as it is a prevalent condition in aging. Covarying multiple other relevant factors, they found direct effects of left CAS on most cognitive tests, except visual memory and construction, which were instead influenced primarily by right CAS. Their findings point to possible new directions in early detection and intervention of cognitive decline and to novel insights into biological asymmetries in brain functioning. Similarly innovative, Wang et al. examined retinal thickness and microvasculature as a rapid, non-invasive, and accessible screening approach to detect impending cognitive decline in middle and older age. Retinal structure and microvasculature were associated with cognition (e.g., processing speed) and hippocampal volume. These studies offer the potential for new insights into early mechanisms and detection of risk for cognitive decline, with approaches that might also better reach underserved populations.

Two studies in the collection examined metabolic factors as indices of cognitive functioning. Ayerdem et al. studied erythropoietin (EPO), a hormone that stimulates red blood cell production, in a large sample of community-dwelling middle-aged and older adults. Higher EPO levels were associated with better complex cognition (executive functioning), suggesting

it may offer neurocognitive protection. Higher serum ferritin, the major iron storage protein, was contrastingly associated with poorer episodic memory. Thus, basic blood-based markers may be able to predict cognitive decline, thereby providing new directions for studying the biological pathways of cognitive aging. Relatedly, Li et al. examined motoric cognitive risk syndrome (MCR; 10% prevalence in older adults), a "pre-dementia syndrome" characterized by slow but unassisted gait and subjective cognitive complaints without dementia. Metabolomic and lipidomic profile analysis revealed distinct metabolic subtypes associated with MCR, as distinguished from the profiles in subjects with cognitive impairment. Their findings shed new light on metabolic contributions to subjective cognitive complaints and risk for cognitive decline, as well as on the mechanisms of MCR.

Insights in neurocognitive markers of AD risk and progression

AD, the most common form of dementia, has no cure or highly effective treatment to stop its progression (Alzheimer's Association., 2022). Three studies in this collection addressed new directions in detection and diagnosis of AD. The first study examined autosomal dominant AD (ADAD; 1% of AD cases, Bekris et al., 2010). ADAD has long asymptomatic and only mildly symptomatic phases (Ryman et al., 2014), thereby allowing study of early biomarkers and pathophysiological changes. Qiu reviewed resting and task-related functional magnetic resonance imaging (fMRI) activity and connectivity studies in ADAD, reporting abnormalities in key hubs in medial temporal lobe, striatum, posterior cingulate, and frontal cortices. Similar patterns were evident in sporadic AD, with both AD types distinguishable from those in typical aging. Inter-network connectivity was also greatest prior to symptom onset, with decreasing connectivity as symptoms progress and age of typical onset approaches. Their findings, if applied in large, multi-center studies, might provide a model for predicting AD onset and progression. Dong et al. examined functional connectivity data using machine learning to predict neuropsychological performance in AD and mild cognitive impairment (MCI) compared with healthy controls. Cognitive impairment was effectively predicted by three networks—central executive, sensorimotor, and default mode. Notably, multiple rather than single networks were implicated in each cognitive domain, suggesting that assessing the extent of multi-network changes might be key to predicting MCI and AD. Lastly, Murakami and Lacayo used the 2022 Reactome pathway knowledgebase and GeneAnalytics to identify and update the current listing of genetic and disease hallmarks for AD. Their work added five new AD biological hallmarks to existing hallmarks. They further showed that AD genes were associated not just with AD but also with >20 diverse age-related diseases and comorbidities, suggesting that various modifiable lifestyle factors are the crucial targets for AD prevention and treatment (Smith et al., 2013).

Insights in lifestyle contributions to cognitive aging and AD

Modifiable lifestyle behaviors (e.g., exercise, diet, social engagement, etc.) have widespread associations with brain functioning that are protective of brain and cognition in aging (McDonough et al., 2020; Soldan et al., 2021; Won et al., 2021); they have been proposed to reduce the risk of dementia by 40% (Livingston et al., 2020). Three papers in this topic collection addressed the influence of lifestyle factors in cognitive aging. Festini's mini-review outlined evidence of the benefits of living a busy and socially, physically, and mentally engaged lifestyle. She also highlighted that the mechanisms underlying these effects are unknown and that since "busyness" is neither inherently beneficial or detrimental on its own, better study designs are needed to decipher the complex inter-relationships amongst busyness, stress, and cognition. Gillespie et al. examined MRI, genetic, and environmental factors on predicted brain age in a large longitudinal sample of male twins. They found early and genetic influences were highly correlated and attributable to a single, common factor that was stable across age and thus, were unlikely to greatly contribute to brain aging. In contrast, individual factors such as relationships, diet, drugs, stressors, and lifestyle activities, were more likely to impact brain age, with negative life events, particularly in interpersonal relationships, most negatively associated with brain age. Finally, Gust et al. illuminated a critical young-old cohort difference that might explain age-related functional connectivity differences: fitness. Baseline data from a 16-week exercise intervention study comparing young and older adults showed that although average connectivity did not differ between the age groups, region-to-region connectivity was weaker within the fronto-parietal and default-mode networks in older adults. After accounting for fitness, age differences were attenuated, suggesting that age-related fitness loss may drive regional interconnectivity changes.

Insights and new avenues in neurocognitive and brain aging theory

At least four major, sometimes opposing, patterns of brain aging are often discussed in the literature: loss of neural distinctiveness, neural inefficiency, neural compensation, and brain maintenance (Dennis and Gutchess, 2020). Three papers in this collection addressed neurocognitive aging theories, highlighting their role in future scientific progress. A review by McDonough et al. noted that many papers report brain aging patterns that have not replicated, or that are potentially mutually exclusive, thereby conflicting with one another. They concluded that no current theory is specific or robust enough to delineate when such patterns will or will not occur in a given sample. They highlighted the need for pre-registration of theories, larger and diverse samples, and explicit testing of theory with specific, directional hypotheses. Similarly, a bibliometric analysis by Othman et al. concluded that no one existing theory fully explains the variability in cognitive aging patterns. They argued that the literature is increasingly scattered, with too few authors making multiple contributions to the field, and for the urgent need to integrate findings with modern theory across multiple major arenas, from individual level processing to risk factors and population studies.

Two review papers in this collection are good examples of the limitations of modern neurocognitive aging theories and their applications. Cansino conducted a systematic review of successful episodic memory retrieval in aging, as measured by functional MRI (fMRI) connectivity. Surprisingly, only twenty studies were

eligible for the review, but unsurprisingly, the majority used the hippocampus as the primary seed, which directed the focus of the analysis. Older adults had decreased hippocampal connectivity with the recollection network (e.g., parahippocampal gyrus, posterior cingulate cortex), but increased connectivity with various distant, task-relevant regions, relative to young adults. She speculated that the latter was compensatory, albeit at heightened cost, to overcome reduced function in the recollection network. Relatedly, Long et al. examined aging across 278 fMRI studies of inhibitory control, a fundamental aspect of executive functioning. Their meta-analysis suggested a core network underlies both cognitive- and response-inhibition, as separate components (e.g., middle cingulate, supplementary motor area, inferior frontal gyrus, inferior parietal lobule, and insula), while some regions had more component-specific roles, such as superior parietal lobule in cognitive inhibition and right inferior frontal gyrus, bilateral insula, and angular gyrus in response inhibition. Moreover, left inferior frontal gyrus, bilateral insula and left superior parietal lobule activation diverged in older adults, being greater during cognitive inhibition but reduced during response inhibition. Thus, with complex conflict processing, flexible regional recruitment appeared limited in older adults. Yet, in both these studies, interpretations were mostly speculative due to studies lacking direct theoretical comparisons and to overlaps of theoretical predictions.

Kremen et al. reviewed the literature on another theoretically important arena of cognitive aging research, cognitive reserve, brain reserve, and resilience. These are hypothetical constructs describing individual differences in the ability of the brain or mind to resist damage and degeneration (Pettigrew and Soldan, 2019; Stern et al., 2020). Due to inconsistencies in the usage of these terms and resulting empirical confounds, the authors proposed new definitions to specify and distinguish reserve, maintenance, and resilience as parallel constructs. They organized these definitions around cognitive reserve, cognitive resilience, and the maintenance of cognitive reserve on the one hand, and brain reserve, brain resilience, and brain maintenance on the other hand. This new framework may guide future research into individual differences in cognitive and brain aging trajectories and the various lifestyle and genetic factors that contribute to them. We note that there is also need for these constructs to better integrate with contemporary brain and cognitive aging theories.

Conclusion

Despite the advances in neuroimaging and the proposal of multiple neurocognitive aging theories, the studies in this inaugural collection highlight that a new frontier is coming. New research is on the cusp of better integrating existing knowledge that will allow researchers to better predict cognitive decline and accompanying brain changes that occur with aging and in age-related diseases on an individual basis, or at least for subsets of individuals (Albert et al., 2018; Paitel and Nielson, 2021). Some of this new research stems from a better understanding of how peripheral organs that interact with the brain can be leveraged. Other approaches highlight the growing need to incorporate adults in middle-age rather than assuming the underlying mechanisms related to cognitive decline and brain alterations start in older age. Doing so pushes the boundary of early detection and moves toward life course approaches to our understanding of neurocognitive aging (McDonough et al., 2019).

Author contributions

KN wrote the first draft of the manuscript. All authors contributed to manuscript additions and revisions, and read and approved the submitted version.

Funding

This work was supported by NIH grants R01-AG022304, R01-AG057552, R21-NS121624, R15-HD093086 (KN), and P30-AG066507 (AS; PI: Albert).

Acknowledgments

We gratefully acknowledge all the authors and reviewers who participated in this Research Topic.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ORIGINAL RESEARCH
published: 08 April 2022
doi: 10.3389/fnagi.2022.862856

Association of Endogenous Erythropoietin Levels and Iron Status With Cognitive Functioning in the General Population

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OPEN ACCESS

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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: 26 January 2022
Accepted: 15 March 2022
Published: 08 April 2022

Citation:
Ayerdem G, Bosma MJ, Vinke JSJ, Ziengs AL, Potgieser ARE, Gansevoort RT, Bakker SJL, De Borst MH and Eisenga MF (2022) Association of Endogenous Erythropoietin Levels and Iron Status With Cognitive Functioning in the General Population. Front. Aging Neurosci. 14:862856. doi: 10.3389/fnagi.2022.862856

Background: Emerging data suggest that erythropoietin (EPO) promotes neural plasticity and that iron homeostasis is needed to maintain normal physiological brain function. Cognitive functioning could therefore be influenced by endogenous EPO levels and disturbances in iron status.

Objective: To determine whether endogenous EPO levels and disturbances in iron status are associated with alterations in cognitive functioning in the general population.

Materials and Methods: Community-dwelling individuals from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a general population-based cohort in Groningen, Netherlands, were surveyed between 2003 and 2006. Additionally, endogenous EPO levels and iron status, consisting of serum iron, transferrin, ferritin, and transferrin saturation were analyzed. Cognitive function was assessed by scores on the Ruff Figural Fluency Test (RFFT), as a reflection of executive function, and the Visual Association Test (VAT), as a reflection of associative memory.

Results: Among 851 participants (57% males; mean age 60 ± 13 years), higher endogenous EPO levels were independently associated with an improved cognitive function, reflected by RFFT scores (ß = 0.09, $P = 0.008$). In multivariable backward linear regression analysis, EPO levels were among the most important modifiable determinants of RFFT scores (ß = 0.09, $P = 0.002$), but not of VAT scores. Of the iron status parameters, only serum ferritin levels were inversely associated with cognitive function, reflected by VAT scores, in multivariable logistic regression analysis (odds ratio, 0.77; 95% confidence interval 0.63–0.95; $P = 0.02$ for high performance on VAT, i.e., ≥11 points). No association between iron status parameters and RFFT scores was identified.

Conclusion: The findings suggest that endogenous EPO levels and serum ferritin levels are associated with specific cognitive functioning tests in the general population. Higher EPO levels are associated with better RFFT scores, implying better executive function.

Serum ferritin levels, but not other iron status parameters, were inversely associated with high performance on the VAT score, implying a reduced ability to create new memories and recall recent past. Further research is warranted to unravel underlying mechanisms and possible benefits of therapeutic interventions.

Keywords: erythropoietin (EPO), iron, cognitive functioning, general population, visual association test, ruff figural fluency test

INTRODUCTION

Erythropoietin (EPO) and iron are the primary regulators of red blood cell production. Besides being the fuel for erythropoiesis, EPO, and iron are known to express a myriad of non-hematopoietic effects (Nekoui and Blaise, 2017). An important non-hematopoietic effect concerns the maintenance of a normal physiological brain function (Ehrenreich et al., 2004; Ji et al., 2017). As a consequence, disturbances in EPO levels and iron status might negatively affect cognitive functioning, which is pivotal to focus, process information, and adapt or maintain a healthy lifestyle (Gill et al., 2020).

EPO receptors (EPOR) are prominently expressed in the brain in glial cells, neurons, and endothelial cells (Konishi et al., 1993; Digicaylioglu et al., 1995; Marti et al., 1996). EPO can pass the blood-brain barrier to exert its effect on the EPOR in the brain (Brines et al., 2000; Ehrenreich et al., 2004; Xenocostas et al., 2005). Moreover, in experimental models, astrocytes have been shown to produce and secrete EPO (Masuda et al., 1994). EPO promotes neural plasticity and has anti-inflammatory, anti-apoptotic, anti-oxidative, angiogenic, and stemcell-modulatory effects (Sirén et al., 2001; Gorio et al., 2002; Springborg et al., 2002; Buemi et al., 2003; Villa et al., 2003; Lykissas et al., 2007; Sargin et al., 2010; Girolamo et al., 2014; Nekoui et al., 2015). Therefore, EPO appears to have neuroprotective and neurotrophic properties, which in turn might hypothetically affect cognitive functioning (Wakhloo et al., 2020). Various studies focusing on different cerebral disease models support such a hypothesis, with some authors reporting that administration of recombinant human EPO (rhEPO) has a positive effect on cognitive functioning (Ehrenreich et al., 2008; Miskowiak et al., 2008, 2012, 2016; Sargin et al., 2010; Nekoui and Blaise, 2017).

Similarly, several studies have shown a relationship between serum iron levels and cognitive functioning (Miskowiak et al., 2012; Ji et al., 2017). Iron is a crucial part of many proteins including heme, iron sulfur clusters, and other functional groups (Schiepers et al., 2010). These proteins are essential for the formation of myelin surrounding axons and adenosine triphosphate in mitochondria, cell signaling, host defense, and nucleic acid replication and repair (Todorich et al., 2009; Mills et al., 2010; Evstatiev and Gasche, 2012). Iron is also crucially involved in the synthesis of several neurotransmitters, including tyrosine hydroxylase (dopamine and norepinephrine) and tryptophan (serotonin) (Moos et al., 2007; Todorich et al., 2009). As iron homeostasis is normally tightly regulated, iron deficiency, and overload affect enzymatic and structural proteins. Indeed, both iron deficiency and iron overload have been implicated in impaired cognitive functioning (Casanova and Araque, 2003; Miskowiak et al., 2012; Ji et al., 2017).

To date, the relationship between EPO levels and iron status with cognitive functioning has only been assessed in experimental models and relatively small sample size populations, often involving specific patient populations, e.g., having mood disorders (Beard et al., 1997; Milward et al., 1999; Weiskopf et al., 2006) questioning the role of endogenous EPO levels and iron status with cognitive functioning in the general population. Hence, we aimed to assess in a large population-based cohort the association between endogenous EPO levels and iron status parameters with cognitive functioning as reflected by two cognitive tests, i.e., the Ruff Figural Fluency Test (RFFT) and the Visual Association Test (VAT).

MATERIALS AND METHODS

Study Design and Population

For this study, we used the PREVEND (Prevention of REnal and Vascular ENd stage Disease) database, a general population-based cohort study. In 1997 and 1998, all inhabitants from the city of Groningen, between the age of 28–75 years (n = 85,421), were sent a short questionnaire and a vial to collect a first-morning void urine sample. 40,856 (48%) people responded. Individuals with insulin-dependent Diabetes Mellitus and pregnant women were excluded. Six thousand subjects with a urinary albumin excretion $\geq$ 10 mg/L and 2,592 randomly selected subjects (control group) with a urinary albumin excretion $<$ 10 mg/L completed the screening protocol and formed the PREVEND cohort baseline (n = 8,592). We used the third survey of PREVEND, which took place between 2003 and 2006. Of these participants, multiple blood samples were collected in which, among others, EPO levels and iron status parameters were measured. Two tests reflecting certain cognitive domains (i.e., RFFT and VAT) were introduced during the same survey. For current analysis, we included 851 patients with data available on EPO levels, iron status, and both cognitive tests (as depicted in **Figure 1**). The PREVEND study protocol was approved by the institutional medical ethical review board of the University Medical Center Groningen and was conducted in accordance with the Helsinki declaration. All subjects provided written informed consent.

Data Collection and Definitions

The procedures at each examination in the PREVEND study have been described in detail previously (Hillege et al., 2001).

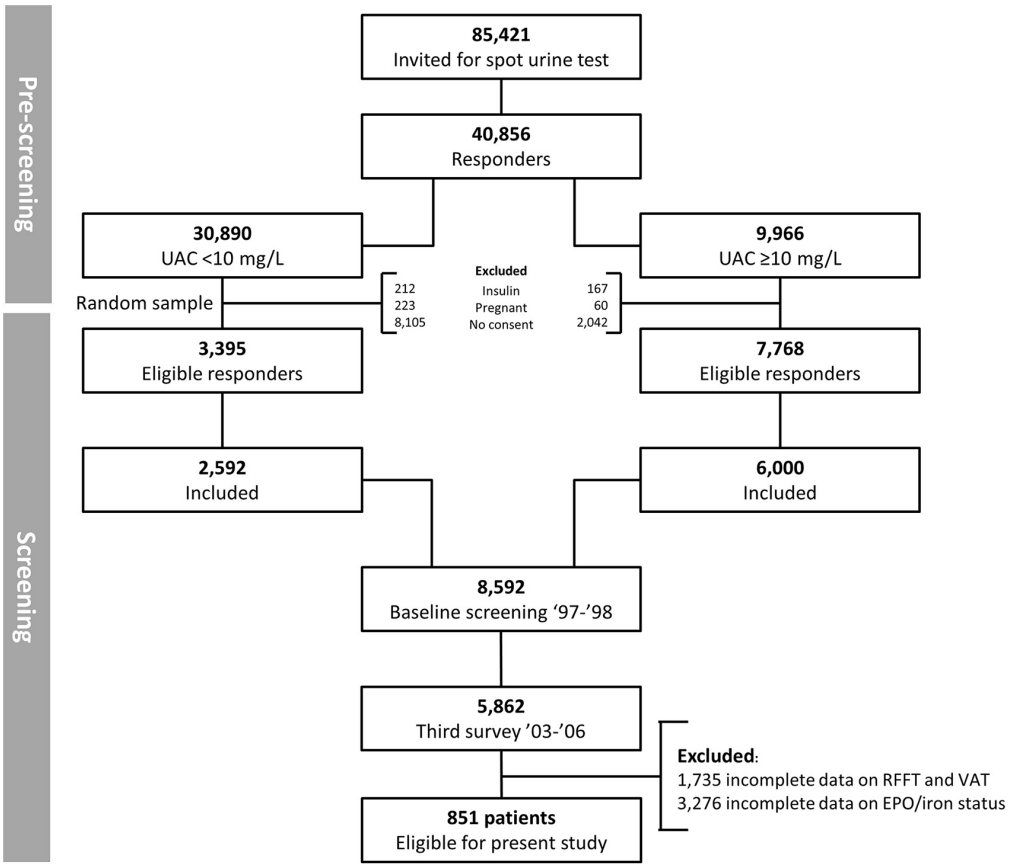

FIGURE 1 | Flowchart of 851 PREVEND participants selected for final analysis.

In short, upon entry into the study, all participants completed a questionnaire regarding demographics, current diagnoses, medical history, smoking habits, alcohol consumption, and medication use. Information on medication use was combined with information from a pharmacy-dispensing registry. Educational level was defined as low (primary education or intermediate vocational education), middle (higher secondary education), and high (higher vocational education and university). Antihypertensives included diuretics, β–blockers, calcium channel blockers, and renin-angiotensin system inhibitors.

Cognitive Function Testing

Ruff Figural Fluency Test

The RFFT measures a subject's ability to produce novel figures utilizing five different dot configurations (Ruff et al., 1987). Participants were instructed to produce as many unique designs as possible using at least two of the dots in a 5-dot matrix. The lowest score is 0 points, the highest and best score is 175 points. The RFFT is a sensitive test for executive cognitive abilities such as non-verbal fluency, planning strategies, task shifting, selective attention, response evaluation, and response suppression, which are necessary to coordinate this process (Mulder et al., 2006). It has been shown to be sensitive to early changes in cognitive function in young as well as middle-aged people (Foster et al., 2005). A reduced ability to produce novel figures can indicate a disability in executive function in general and has been linked to processes in the frontal lobe, most prominently in the right frontal lobe (Ruff et al., 1994; Mulder et al., 2006).

Visual Association Test

The VAT is a brief episodic memory test presenting six paired pictures of two interacting objects where one has to name the missing object on a cue card which has been shown before. One point is given if the missing object is correctly identified. The minimum score is 0 points; the maximum score is 12 points. The test is used to detect anterograde amnesia and related syndromes, usually associated with atrophy of the (medial-temporal areas of the) limbic system. It is hypothesized that a low score on the VAT is related to impaired ability in coding new information or, less likely, in short-term memory (Lindeboom et al., 2002).

Measurements

Fresh fasting blood samples were collected in the morning from all participants and stored at −80°C. EPO was measured using an immunoassay based on chemiluminescence (Immulite EPO assay, DPC, Los Angeles, CA, United States). Serum iron, ferritin, and transferrin were measured using colorimetrix

assay, immunoassay, or immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany), respectively. Transferrin saturation (TSAT,%) was calculated as 100 × serum iron (μmol/L)÷(25 × transferrin[g/L]). A Coulter Counter STKS sum was used to measure hemoglobin (g/dL) (Coulter Corporation, Miami, FL, United States). Serum creatinine was measured using an enzymatic method on a Roche Modular analyzer (Roche Diagnostics). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate the estimated glomerular filtration rate (eGFR) (Levey et al., 2009). Urinary albumin concentration was determined by nephelometry (BN II, Dade Behring Diagnostica, Marburg, Germany). Urinary albumin excretion (UAE) was calculated as the average UAE in the two consecutive 24-h urine collections. Body mass index (BMI) was calculated as the ratio of weight divided by height squared (kg/m^2). High-sensitivity C-reactive protein (hs-CRP), cholesterol, high- density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured using routine laboratory procedures.

Statistical Analysis

Data were analyzed using IBM SPSS, version 23.0 (SPSS, Chicago, IL, United States) and R version 4.0.2 (Vienna, Austria). Baseline characteristics were described as means with standard deviation when normally distributed and medians with interquartile range when distributions were skewed. Categorical variables were reported using numbers (percentage). We described baseline characteristics both for the total population and across quartiles of EPO and ferritin levels. Differences between the quartiles were calculated using analysis of variance (ANOVA), Kruskal-Wallis test or χ2-test, as appropriate. In regression analysis, we determined if serum EPO levels and iron status parameters can be regarded as important determinants of cognitive capacity domains measured by the RFFT and VAT. Univariable linear regression analysis was performed of all included factors with RFFT as the dependent variable. Subsequently, we performed multivariable-adjusted models and multivariable backward linear regression analysis (entry and exit level set at $P < 0.2$ and $P < 0.1$, respectively). In all regression analyses, skewed variables were naturally log-transformed. In the multivariable model, we adjusted for age, sex, education, BMI, eGFR, and urinary albumin excretion (model 1); for systolic blood pressure, alcohol use, smoking, hemoglobin, hs-CRP, serum HDL, and serum LDL levels (model 2); and for history of a myocardial or cerebrovascular event, diabetes mellitus, and the use of antihypertensives, and lipid lowering drugs (model 3). Due to the skewed distribution, the VAT scores were dichotomized and divided at the median into high performance (≥11 points) and low performance (≤10 points), in line with previous investigations of the VAT score (Joosten et al., 2014). The association of EPO levels and iron status parameters were evaluated by logistic regression analysis in a similar way. In multiple regression analyses, iron status parameters were assessed separately due to multi-collinearity between the iron status parameters. The contribution of EPO levels was reported with ferritin levels as only iron status parameter in all models. Statistical significance was considered as a two-tailed p-value of <0.05.

RESULTS

Study Population

We included 851 participants (57% males) with a mean age of 60.3 ± 13.0 years. Participants had a mean BMI of 27.1 ± 3.9 kg/m^2 and an eGFR of 85.5 ± 19.5 ml/min/1.73m^2. A majority of the participants [412 (48%)] registered a low educational level, whereas 226 (27%) and 213 (25%) had a middle and high educational level, respectively. The median EPO level in the total population was 7.8 (5.9–10.1) IU/L; median ferritin concentration was 117 (58–197) μg/L; mean iron level was 16.3 ± 5.2 μmol/L; mean transferrin level was 2.5 ± 0.4 g/L; and mean TSAT was 26.4 ± 9.2%. Further baseline demographics, clinical characteristics, and laboratory parameters according to quartiles of EPO and ferritin levels in the total population are depicted in **Tables 1**, **2**, respectively.

Ruff Figural Fluency Test and Visual Association Test Scores in the Total Population

Participant scored an average of 62 ± 25 points on the RFFT. If compared to the norm score, 672 (79%) scored average on the RFFT, 85 (10%) above average, 68 (8%) below average, and 26 (31%) participants had a deviant. Participants obtained a median VAT score of 10 points (IQR = 8–11). Considering the norm, 684 (80%) participants scored average on the VAT, 107 (12.6%) above average, 42 (5%) below average, and 18 (2%) people had a deviant.

Erythropoietin, Iron Status, and Ruff Figural Fluency Test Score

Across quartiles of serum EPO levels, we noticed a significant inverse association with RFFT score. Individuals in the lowest quartile of EPO levels had 63.9 ± 26.2 points, whereas participants in the upper quartile of EPO scored 61.9 ± 25.7 points on the RFFT ($P < 0.001$). Similarly, we identified a significant inverse association, even more pronounced, across quartiles of ferritin levels. Participants within the lowest quartile of ferritin obtained 67.5 ± 26.2 points, whereas participants in the highest quartile of ferritin obtained 57.3 ± 23.2 points on the RFFT ($P < 0.001$).

In multivariable linear regression analysis, EPO levels were significantly associated with RFFT scores independent of potential confounders (fully adjusted ß = 0.09, $P = 0.008$ as depicted in model 3; **Table 3**). None of the iron status parameters, including serum ferritin, were significantly associated with RFFT scores.

In multivariable linear backward regression analysis, EPO levels were among the main determinants of RFFT (β = 0.09, $P = 0.002$). In contrast, none of the iron status parameters was significantly associated with RFFT (**Table 4**).

Erythropoietin, Iron Status, and Visual Association Test

Across quartiles of EPO, we identified no significant differences in VAT score ($P = 0.79$). In contrast, we

TABLE 1 | Baseline characteristics of 851 community-dwelling subjects according to quartiles of EPO levels.

		EPO quartiles				
	Overall	**Q1**	**Q2**	**Q3**	**Q4**	***p*-value**
	***N* = 851**	**213**	**213**	**214**	**211**	
	(range)	**(1.6–5.9)**	**(5.9–7.8)**	**(7.8–10.1)**	**(10.2–99.4)**	
Cognitive tests						
VAT	10 (8–11)	10 (8–11)	10 (8–11)	10 (8–11)	10 (8–11)	0.79
High performance on VAT (n,%)	297 (35%)	82 (38%)	69 (32%)	75 (35%)	71 (34%)	0.58
RFFT	62 ± 25	63.9 ± 26.2	61.7 ± 24.3	62.1 ± 25.5	61.9 ± 25.7	<0.001
Age	60.3 ± 13	57.5 ± 12.6	59.7 ± 12.9	60.7 ± 12.8	63.2 ± 13.1	<0.001
Male sex (n,%)	485 (57%)	112 (53%)	118 (55%)	132 (62%)	123 (58%)	0.26
Education						0.71
Low (n,%)	412 (48%)	103 (48%)	104 (49%)	105 (49%)	100 (47%)	
Middle (n,%)	226 (27%)	50 (23%)	54 (25%)	63 (29%)	59 (28%)	
High (n,%)	213 (25%)	60 (28%)	55 (26%)	46 (21%)	52 (25%)	
Medication use						
Antihypertensives (n,%)	254 (31%)	47 (22%)	57 (28%)	67 (32%)	83 (40%)	0.001
Lipid lowering (n,%)	141 (17%)	19 (9%)	37 (18%)	37 (18%)	48 (23%)	0.002
Iron suppletion (n,%)	2 (<1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0.11
Health behavior and medical history						
BMI (kg/m^2)	27.2 ± 3.7	26.3 ± 3.5	26.9 ± 3.8	27.1 ± 4.1	28 ± 4.1	<0.001
Systolic blood pressure (mmHg)	130 ± 19	125 ± 17	129 ± 18	130 ± 17	135 ± 21	<0.001
Alcohol use (n,%)	641 (76%)	175 (83%)	170 (81%)	152 (72%)	144 (68%)	0.001
Smoking (n,%)	164 (19%)	55 (26%)	39 (18%)	36 (17%)	34 (16%)	0.04
Cardiac event[a] (n.%)	24 (3%)	4 (2%)	5 (2%)	6 (3%)	9 (4%)	0.48
Cerebrovascular event[b] (n,%)	15 (2%)	2 (1%)	7 (3%)	3 (1%)	3 (1%)	0.26
Diabetes Mellitus[c] (n,%)	82 (10%)	18 (9%)	19 (9%)	16 (8%)	29 (14%)	0.13
Laboratory measurements						
EPO (IU/L)	7.8 (5.9–10.1)	4.8 (4.1–5.4)	6.9 (6.4–7.3)	8.9 (8.3–9.3)	12.9 (11.4–15.7)	–
Iron status						
Ferritin (μg/L)	117 (58–197)	125 (77–213)	117 (70–197)	119.5 (58–204)	93 (32–178)	0.001
Iron (μmol/L)	16.3 ± 5.2	17.4 ± 4.9	16.9 ± 5.2	16.2 ± 4.8	14.7 ± 5.5	<0.001
Transferrin (g/L)	2.5 ± 0.4	2.5 ± 0.3	2.5 ± 0.4	2.5 ± 0.4	2.6 ± 0.5	0.05
Transferrin saturation (%)	26 ± 9	28 ± 9	28 ± 9	26 ± 8	23 ± 10	<0.001
Hemoglobin (g/dL)	13.9 ± 1.1	14.0 ± 1.1	14.0 ± 1.1	13.9 ± 1.1	13.4 ± 1.3	<0.001
MCV (fL)	90.1 ± 4.2	89.4 ± 3.8	90.2 ± 3.6	90.1 ± 4	90.7 ± 5.2	0.02
eGFR (ml/min/1.73m^2)	86 ± 20	89 ± 19	87 ± 19	86 ± 19	81 ± 21	<0.001
Urinary albumin excretion (mg/24 h)	9.5 (6.6–20.8)	9.1 (6.6–15.2)	9.4 (6.5–17.8)	9.2 (6.4–23.3)	11 (7.1–28.3)	0.008
hs-CRP (mg/L)	1.3 (0.6–2.4)	1.2 (0.6–2.1)	1.2 (0.6–2.2)	1.2 (0.6–2.1)	1.5 (0.7–3.7)	0.001
Cholesterol (mmol/L)	5.4 ± 1.1	5.6 ± 1	5.4 ± 1.1	5.4 ± 1	5.2 ± 1.1	0.003
HDL (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	0.70
LDL (mmol/L)	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1 ± 0.3	1 ± 0.4	0.04
Triglycerides (mmol/L)	1.2 (0.9–1.7)	1.3 (1–1.8)	1.2 (0.9–1.7)	1.3 (0.9–1.6)	1.2 (0.9–1.7)	0.19

Data are expressed as mean ± standard deviation, median (interquartile range), or proportion n (%). Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; MCV, mean corpuscular volume; RFFT, Ruff Figural Fluency Test; VAT, Visual Association Test. [a]Cardiac event included a history of myocardial infarction and ischemic heart disease, [b]cerebrovascular event included a history of subarachnoid hemorrhage, intra-cerebral hemorrhage, other and unspecified intracranial hemorrhage, and occlusion and stenosis of pre-cerebral or cerebral arteries, [c]not-insulin dependent diabetes mellitus.

identified that the prevalence of high performance scores (i.e., ≥11 points) was significantly different across quartiles of ferritin levels. Of the participants within the lowest quartile of ferritin, 46% had a high performance score, whereas only 25% of the participants within the upper quartile of ferritin had a high performance score ($P < 0.001$).

In multivariable logistic regression analysis, EPO levels were not significantly associated with a high performance on the VAT. Of the iron status parameters, only serum ferritin was

TABLE 2 | Baseline characteristics of 851 community-dwelling subjects according to quartiles of ferritin levels.

		Ferritin quartiles				
	Overall	**Q1**	**Q2**	**Q3**	**Q4**	***P*-value**
	***N* = 851**	**214**	**214**	**213**	**210**	
	(range)	**(4.0–58.0)**	**(59.0–117.0)**	**(118.0–197.0)**	**(198.0–1309.0)**	
Cognitive tests						
VAT	10 (8–11)	10 (9.0–11)	10 (8–11)	10 (8–11)	9 (7–10)	<0.001
High performance on VAT (n,%)	297 (35%)	99 (46%)	74 (35%)	72 (34%)	52 (25%)	<0.001
RFFT	62 ± 25	67.5 ± 26.2	66.4 ± 25.2	58.4 ± 25.4	57.3 ± 23.2	<0.001
Age	60.3 ± 13	55.4 ± 13.3	59.4 ± 12.4	63.2 ± 12.3	63.2 ± 12.4	<0.001
Male sex (n,%)	485 (57%)	75 (35%)	118 (55%)	131 (62%)	131 (62%)	<0.001
Education						0.21
Low (n,%)	412 (48%)	94 (44%)	103 (48%)	111 (52%)	104 (50%)	
Middle (n,%)	226 (27%)	58 (27%)	54 (25%)	63 (30%)	51 (24%)	
High (n,%)	213 (25%)	62 (29%)	57 (27%)	39 (18%)	55 (26%)	
Medication use						
Antihypertensives (n,%)	254 (31%)	39 (19%)	51 (25%)	76 (36%)	88 (43%)	<0.001
Lipid lowering (n,%)	141 (17%)	15 (7%)	35 (17%)	43 (20%)	48 (24%)	<0.001
Iron suppletion (n,%)	2 (<1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0.57
Health behavior and medical history						
BMI (kg/m^2)	27.1 ± 3.9	26.2 ± 4	26.6 ± 3.7	27.2 ± 3.7	28.5 ± 3.8	<0.001
Systolic blood pressure (mmHg)	130 ± 19	125 ± 18	127 ± 17	132 ± 20	135 ± 18	<0.001
Alcohol use (n,%)	641 (76%)	143 (67%)	170 (80%)	160 (76%)	168 (81%)	0.002
Smoking (n,%)	164 (19%)	50 (23%)	54 (25%)	35 (17%)	25 (12%)	0.001
Cardiac event[a] (n.%)	24 (3%)	5 (2%)	8 (4%)	4 (2%)	7 (3%)	0.63
Cerebrovascular event[b] (n,%)	15 (2%)	2 (1%)	3 (1%)	5 (2%)	5 (2%)	0.60
Diabetes Mellitus[c] (n,%)	82 (10%)	15 (7%)	12 (6%)	20 (10%)	35 (17%)	<0.001
Laboratory measurements						
EPO (IU/L)	7.8 (5.9–10.1)	8.6 (6.4–12.3)	7.4 (5.8–9.6)	7.5 (5.7–9.7)	7.7 (5.7–9.7)	<0.001
Iron status						
Ferritin (μg/L)	117 (58–197)	32.5 (22–45)	88 (75–101)	150 (131–173)	273 (230–355)	–
Iron (μmol/L)	16.3 ± 5.2	14.9 ± 5.9	16.1 ± 4.5	16.6 ± 4.9	17.8 ± 5.1	<0.001
Transferrin (g/L)	2.5 ± 0.4	2.8 ± 0.4	2.5 ± 0.3	2.4 ± 0.3	2.4 ± 0.3	<0.001
Transferrin saturation (%)	26 ± 9	22 ± 9	26 ± 8	28 ± 9	30 ± 10	<0.001
Hemoglobin (g/dL)	13.9 ± 1.1	13.2 ± 1.1	13.9 ± 1.1	13.9 ± 1.1	14.2 ± 1.1	<0.001
MCV (fL)	90.1 ± 4.2	89.3 ± 4.4	90.4 ± 4.0	90.0 ± 4.1	90.8 ± 4.2	0.003
eGFR (ml/min/1.73m^2)	86 ± 20	90 ± 19	86 ± 20	82 ± 19	83 ± 20	<0.001
Urinary albumin excretion (mg/24 h)	9.5 (6.6–20.8)	8.8 (6.2–17.6)	8.7 (6.6–15.2)	9.5 (6.5–20.6)	12.2 (7.4–28.3)	<0.001
hs-CRP (mg/L)	1.3 (0.6–2.4)	1.2 (0.6–2.6)	1.2 (0.6–2.3)	1.25 (0.61–2.12)	1.4 (0.7–3.2)	0.17
Cholesterol (mmol/L)	5.4 ± 1.1	5.4 ± 1.2	5.5 ± 1.1	5.4 ± 1.0	5.4 ± 1.0	0.68
HDL (mmol/L)	1.4 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	<0.001
LDL (mmol/L)	1.1 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	<0.001
Triglycerides (mmol/L)	1.2 (0.9–1.7)	1.1 (0.8–1.5)	1.2 (0.9–1.5)	1.3 (1.0–1.7)	1.4 (1.1–1.9)	<0.001

Data are expressed as mean ± standard deviation, median (interquartile range) or proportion n (%). Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; MCV, mean corpuscular volume; RFFT, Ruff Figural Fluency Test; VAT, Visual Association Test. [a]Cardiac event included a history of myocardial infarction and ischemic heart disease, [b]cerebrovascular event included a history of subarachnoid hemorrhage, intra-cerebral hemorrhage, other and unspecified intracranial hemorrhage, and occlusion and stenosis of pre-cerebral or cerebral arteries, [c]not-insulin dependent diabetes mellitus.

significantly inversely associated with a high performance on the VAT (fully adjusted OR, 0.77; 95% CI 0.63 – 0.95; $P = 0.02$ as depicted in model 3, **Table 5**). In contrast, serum iron, transferrin, and TSAT were not associated with a high performance on the VAT score (**Table 5**).

DISCUSSION

In this study, we show that in the general population higher endogenous EPO levels are associated with better executive function, reflected by RFFT scores, whereas higher ferritin levels,

TABLE 3 | Univariate and backward linear regression analyses of potential determinants of RFFT scores.

	Univariate analysis		Backward analysis	
	Std. β	***P*-value**	**Std. β**	***P*-value**
Age	−0.54	<0.001	−0.44	<0.001
Male sex	0.02	0.54		
Education				
Low	−0.35	<0.001	***Ref.***	
Middle	0.08	0.02	0.14	<0.001
High	0.32	<0.001	0.26	<0.001
Medication use				
Antihypertensives	−0.30	<0.001	−0.05	0.13
Lipid lowering	−0.15	<0.001		
Iron suppletion	−0.24	0.49		
Health behavior and medical history				
BMI (kg/m^2)	−0.24	<0.001	−0.05	0.09
Systolic blood pressure (mmHg)	−0.28	<0.001		
Alcohol use (n,%)	0.25	<0.001	0.11	<0.001
Smoking (n,%)	−0.03	0.42		
Cardiac event (n,%)	−0.11	0.001		
Cerebrovascular event (n,%)	−0.05	0.12		
Diabetes Mellitus (n,%)	−0.19	<0.001		
Laboratory measurements				
EPO (IU/L)[a]	−0.03	0.45	0.09	0.002
Iron status				
Ferritin (μg/L)	−0.18	<0.001		
Iron (μmol/L)	−0.01	0.67		
Transferrin (g/L)	0.07	0.05		
Transferrin saturation (%)	−0.04	0.30		
Hemoglobin (mmol/L)	−0.008	0.81		
MCV (fL)	−0.006	0.86		
eGFR (ml/min/1.73m^2)	0.41	<0.001		
Urinary albumin excretion (mg/24 h)	−0.22	<0.001		
hs-CRP (mg/L)	−0.23	<0.001	−0.05	0.15
Cholesterol (mmol/L)	0.05	0.18	0.05	0.09
HDL (mmol/L)	0.15	<0.001	0.05	0.11
LDL (mmol/L)	−0.09	0.01		
Triglycerides (mmol/L)	−0.02	0.67		

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; MCV, mean corpuscular volume; Std. β, Standardized beta; RFFT, Ruff Figural Fluency Test; Ref., reference category.
[a]*Adjusted for only ferritin as iron status parameter.*

but not other iron status parameters, are associated with a lower VAT score, reflecting associative memory. To the best of our knowledge, this is the first study to show associations between serum EPO and ferritin levels and specific domains of cognitive functioning in the general population.

It has been suggested that EPO exerts a protective effect on cognitive functioning due to its neuroprotective and neurotrophic potential (Sirén et al., 2001; Gorio et al., 2002; Springborg et al., 2002; Buemi et al., 2003; Villa et al., 2003; Lykissas et al., 2007; Sargin et al., 2010; Girolamo et al., 2014; Nekoui et al., 2015). The latter has mainly been concluded based on studies in which exogenous EPO was administered (Ehrenreich et al., 2008; Nekoui and Blaise, 2017). Specifically, these studies showed an increase in cognitive function test scores. Here, we demonstrate that higher endogenous EPO levels are associated with better RFFT scores, reflecting improved executive function with improved capabilities such as non-verbal fluency, planning strategies, task shifting, selective attention, response evaluation, and response suppression, which are necessary to coordinate this process (Mulder et al., 2006). This is in line with the hypothesis based on earlier findings of EPO and EPOR expression in (mammalian) brain areas related to executive functioning, and with studies by Ehrenreich et al. and Miskowiak et al. in which exogenous EPO increased several of these (or related) executive functions (Digicaylioglu et al., 1995; Marti et al., 1996; Ehrenreich et al., 2007a,b; Miskowiak et al., 2008, 2014; Nowrangi et al., 2014). Importantly, the effect of high endogenous EPO levels on RFFT scores seems to be independent of the effect of EPO on hematopoiesis, as adjustment for hemoglobin levels did not alter the association. The latter suggests a direct neurobiological effect of EPO on cognition, most likely because of its neuroprotective and neurotrophic potential as an underlying mechanism, which is in line with the long-term impact of EPO on cognition in several other studies (Ehrenreich et al., 2007a,b; Miskowiak et al., 2014).

The exact biological relevance of our endogenous serum EPO levels is difficult to interpret in the absence of a direct measurement of EPO in the brain. EPO is known to cross the blood-brain barrier by active translocation, most likely *via* EPOR expressed in the brain vasculature pattern (Brines et al., 2000). The studies who investigated the neuroprotective and neurotrophic potential of exogenous EPO administered high-dose EPO to induce significant elevations in cerebrospinal fluid and brain EPO levels to improve cognitive function. However, the importance of endogenous circulating EPO levels has also previously been shown in children with malaria where high EPO levels were associated with a reduced risk of neurological sequelae (Casals-Pascual et al., 2008). Similarly, in a recent study, Shim et al. (2021) showed the relationship between circulating EPO levels and attention deficit hyperactivity disorder (ADHD) rating scale in children with ADHD and healthy controls.

We did not find an association between endogenous EPO levels and performance on the VAT, suggesting that endogenous EPO levels did not affect the ability to create new memories and to recall the recent past. Aside from a few exceptions, this runs counter to reports that exogenous EPO improves certain memory-related abilities, as can be seen through upregulation of activity during memory tasks (Ehrenreich et al., 2007b; Miskowiak et al., 2008, 2009, 2014) and upregulation of memory-related brain areas during a memory task (Miskowiak et al., 2007, 2016). With evidence of EPO and EPOR being present in brain areas related to memory, e.g., the hippocampus and areas within the temporal lobe, we expected a positive association of endogenous EPO levels on the VAT score (Digicaylioglu et al., 1995; Marti et al., 1996; Rombouts et al., 1997). The discrepancy between our currently identified results and those from other studies might be related to the use of different populations in

TABLE 4 | Multivariate linear regression analyses of the association of individual iron status parameters and erythropoietin with RFFT score.

	Model 1[a]		Model 2[b]		Model 3[c]	
	Std. β	***P*-value**	**Std. β**	***P*-value**	**Std. β**	***P*-value**
EPO (IU/L)[d]	0.07	0.03	0.09	0.005	0.09	0.008
Ferritin (ug/L)	0.004	0.90	−0.01	0.66	−0.02	0.48
Iron (umol/L)	−0.01	0.71	−0.02	0.50	−0.03	0.38
Transferrin (g/L)	−0.007	0.79	−0.004	0.88	0.005	0.87
TSAT (%)	−0.01	0.67	−0.02	0.49	−0.04	0.26

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; RFFT, Ruff figural fluency test; Std. β, standardized beta; TSAT, transferrin saturation.
[a]*Model 1: adjusted for age, sex, education, BMI, eGFR, and urinary albumin excretion.*
[b]*Model 2: Model 1 + adjustment for systolic blood pressure, alcohol use, smoking, hemoglobin, hs-CRP, serum HDL, serum LDL.*
[c]*Model 3: Model 2 + adjustment for history of cerebrovascular event, diabetes mellitus, and use of antihypertensives, and lipid-lowering drugs.*
[d]*Adjusted for only ferritin as iron status parameter.*

TABLE 5 | Binomial logistic regression analyses of the association of individual iron status parameters and erythropoietin with a high performance on the VAT score.

	Model 1[a]			Model 2[b]			Model 3[c]		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
EPO (IU/L)[d]	0.92	0.65–1.31	0.65	1.05	0.71–1.54	0.81	1.01	0.68–1.51	0.95
Ferritin (ug/L)	0.79	0.65–0.95	0.01	0.78	0.63–0.95	0.01	0.77	0.63–0.95	0.02
Iron (umol/L)	0.99	0.96–1.02	0.37	0.99	0.96–1.02	0.37	0.98	0.95–1.02	0.27
Transferrin (g/L)	1.15	0.77–1.72	0.50	1.04	0.68–1.59	0.86	1.02	0.66–1.58	0.91
TSAT (%)	0.99	0.97–1.01	0.32	0.99	0.98–1.01	0.46	0.99	0.97–1.01	0.33

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; OR, odds ratio; TSAT, transferrin saturation; VAT, Visual association test.
[a]*Model 1: adjusted for age, sex, education, BMI, eGFR, and urinary albumin excretion.*
[b]*Model 2: Model 1 adjustment for systolic blood pressure, alcohol use, smoking, hemoglobin, hs-CRP, serum HDL, and serum LDL.*
[c]*Model 3: Model 2 adjustment for history of cerebrovascular event, diabetes mellitus, and use of antihypertensives, and lipid-lowering drugs.*
[d]*Adjusted for only ferritin as iron status parameter.*

earlier studies, which focused on subjects with depression or schizophrenia.

Moreover, and more likely, the VAT is designed to detect anterograde amnesia and related syndromes. It is a relatively simple task with a small range in scores compared to the RFFT and less suitable to detect subtle differences in memory ability.

Regarding iron status, we did not identify a U-shaped association between iron status and cognitive function, as might have been expected, since previous studies related both a low and high serum iron to a decline in certain cognitive abilities (Lam et al., 2008; Schiepers et al., 2010; Ji et al., 2017). However, we did find that higher ferritin levels increased the risk of a low performance on the VAT. This suggests that increased ferritin levels in the general population are associated with a diminished ability to create new memories and recall the recent past. Since serum ferritin is not related to the iron content in brain regions involved in memory abilities, like the hippocampus and temporal cortex (Gao et al., 2017), the underlying mechanism is not clear. Our finding is contrary to the few previous studies on serum ferritin levels and cognition. Schiepers et al. (2010) found that higher serum ferritin was associated with decreased speed of cognitive functioning, but did not find serum ferritin to be related to memory processes. Milward et al. (2010) found that abnormal levels of ferritin were not associated with global cognitive performance or executive function. When considering serum ferritin as a proxy for body iron stores, our findings are in line with research by Lam et al. (2008), in which very high serum iron concentrations were associated with poorer outcomes on tests measuring short and long-term memory processes. However, caution is warranted to consider serum ferritin solely as surrogate for body iron stores. Serum ferritin is also an acute-phase reactant, which is upregulated by inflammation, excessive use of alcohol, metabolic syndrome, and tissue damage or turnover (e.g., hepatic or malignancy) (Cullis et al., 2018). Previous studies suggest an association with cognitive decline and (biomarkers of) inflammation (Yaffe et al., 2003; Schram et al., 2007; Sartori et al., 2012). Similar associations are seen with direct or indirect effects of alcohol use, metabolic syndrome, tissue damage, -turnover, or a combination (Brust, 2010; Yates et al., 2012; Janelsins et al., 2014; Nardelli et al., 2019). Notably, the association between serum ferritin and VAT remained independent of adjustment for alcohol use, BMI, hemoglobin, and hs-CRP. Although we tried to fully adjust for these potential confounders, we cannot exclude that these mechanisms, at least in part, might have contributed to the identified association between higher ferritin and lower performance on the VAT score. In the patient setting of neurodegenerative diseases, strong associations of cerebrospinal fluid ferritin have been identified with worse cognitive function

in patients with Alzheimer's disease, patients with Parkinson's disease, and patients with dementia with Lewy bodies (Ayton et al., 2022). In fact, cerebrospinal fluid ferritin levels even predicted outcomes in patients with Alzheimer's disease (Ayton et al., 2015, 2017), and could be used as a readout for the inflammatory response during the neurodegenerative phase of Alzheimer's disease (Brosseron et al., 2021).

Our study has several strengths and limitations. We used a well-phenotyped large cohort of community-dwelling individuals, reflecting a large proportion of the general Dutch population. Moreover, we tried to account as fully as possible for confounders as cognitive functioning is known to be influenced by multiple factors. Limitations of the current study are that cognitive functioning was measured only with two tests, which cover a diverse set of cognitive capabilities but do not reflect performance on all cognitive domains. Although the RFFT is a more sensitive and reliable test for detecting subtle changes in cognitive functioning in both young and old people when compared to tests like the Mini Mental State Examination (MMSE), Trail-Making Test (TMT) or Modified Telephone Interview for Cognitive Status (TICS-M) (Foster et al., 2005; Izaks et al., 2011; Joosten et al., 2014), we are not able to extend our findings to cognitive functioning as a whole. Other tests, e.g., the Rey Auditory Verbal Learning Test (RAVLT) and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) would have given important additional information on cognitive functioning. Another limitation is that we did not have data available on a broader range of iron status parameters, such as hepcidin and soluble transferrin receptor. Finally, a limitation of our study is that we did not identify with biomarkers participants with underlying Alzheimer's disease and that we did not have availability of a direct measurement of EPO or ferritin in the brain.

In conclusion, this study demonstrates a relatively strong association between higher endogenous EPO levels and better performance on several executive cognitive abilities, as reflected by the RFFT, in the general population. Furthermore, we found that ferritin levels, but not other iron status parameters, were inversely associated with a high performance on VAT scores, reflecting associative memory. Future research should focus on a more comprehensive examination of cognitive functioning, time-dependent relationships, underlying mechanisms, use of brain imaging, identification of patients with Alzheimer's disease, and opportunities and obstacles for therapeutic interventions.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Public sharing of individual participant data was not included in the informed consent form of the study, but data can be made available to interested researchers upon reasonable request. Requests to access these datasets should be directed to the data manager of the PREVEND study, Dr. Lyanne Kieneker, l.m.kieneker@umcg.nl.

ETHICS STATEMENT

The study involving human participants was reviewed and approved by Institutional Medical Ethical Review Board of the University Medical Center Groningen. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ME realized the research idea and study design and provided supervision and mentorship. GA, MB, SB, and ME carried out data acquisition. GA, MB, and ME carried out statistical analysis. All authors performed the data analysis/interpretation, contributed to important intellectual content during manuscript drafting or revision, and agreed to be personally accountable for the individual's own contributions and to ensured that questions pertaining to the accuracy or integrity of any portion of the work, even on in which the author was not directly involved, were appropriately investigated and resolved, including documentation in the literature if appropriate.

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Conflict of Interest: JV received consultancy fees from Vifor Pharma. MD has received consultancy fees from Astellas, Kyowa Kirin, Pharmacosmos, Sanofi Genzyme, and Vifor Pharma (all to employer), grant support from Sanofi Genzyme and Vifor Pharma. ME received speakers' and consultancy fees from Vifor Pharma and served the Advisory Board of Cablon Medical.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 15 April 2022
doi: 10.3389/fnagi.2022.831002

The Impact of Genes and Environment on Brain Ageing in Males Aged 51 to 72 Years

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Magnetic resonance imaging data are being used in statistical models to predicted brain ageing (PBA) and as biomarkers for neurodegenerative diseases such as Alzheimer's Disease. Despite their increasing application, the genetic and environmental etiology of global PBA indices is unknown. Likewise, the degree to which genetic influences in PBA are longitudinally stable and how PBA changes over time are also unknown. We analyzed data from 734 men from the Vietnam Era Twin Study of Aging with repeated MRI assessments between the ages 51–72 years. Biometrical genetic analyses "twin models" revealed significant and highly correlated estimates of additive genetic heritability ranging from 59 to 75%. Multivariate longitudinal modeling revealed that covariation between PBA at different timepoints could be explained by a single latent factor with 73% heritability. Our results suggest that genetic influences on PBA are detectable in midlife or earlier, are longitudinally very stable, and are largely explained by common genetic influences.

Keywords: predicted brain ageing, twin, gene, longitudinal predicted brain aging, MRI, development, cognitive decline, Alzheimers's disease

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Edited by:
Ashok Kumar,
University of Florida, United States

Reviewed by:
Jacob Raber,
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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *07 December 2021*
Accepted: *15 March 2022*
Published: *15 April 2022*

Citation:
Gillespie NA, Hatton SN, Hagler DJ Jr, Dale AM, Elman JA, McEvoy LK, Eyler LT, Fennema-Notestine C, Logue MW, McKenzie RE, Puckett OK, Tu XM, Whitsel N, Xian H, Reynolds CA, Panizzon MS, Lyons MJ, Neale MC, Kremen WS and Franz C (2022) The Impact of Genes and Environment on Brain Ageing in Males Aged 51 to 72 Years. Front. Aging Neurosci. 14:831002. doi: 10.3389/fnagi.2022.831002

INTRODUCTION

Brain magnetic resonance imaging (MRI) data are increasingly used to predict brain ageing. In turn, predicted brain ageing (PBA) is being used to estimate lifespan, to characterize accelerated ageing, and to identify individuals with mild cognitive impairment and the likelihood of progression to dementia including Alzheimer's Disease (Deary et al., 2009; Salthouse, 2010; Vos et al., 2012; Gaser et al., 2013; Fjell et al., 2014; Lowe et al., 2016; Liem et al., 2017; Cole et al., 2019; Elliott et al., 2019; de Lange and Cole, 2020). This approach works by relying on machine learning to estimate associations between imaging data and chronological age in training samples of varying ages (Cole and Franke, 2017). Using supervised learning algorithms, these associations are then applied to estimate PBA or predicted brain age difference (PBAD) (the difference between predicted and chronological age) in independent samples. Not only does the approach assume that MRI of neuroanatomical degeneration reflects poorer brain health and risk of neurodegenerative diseases (McEvoy et al., 2009; Cole et al., 2019; Wang et al., 2019) but that individual differences in brain aging stem from biological processes influencing lifespan and age-related diseases explained by genetic and environmental influences (Cole et al., 2019). However, very little is known about the relative contribution of genetic and environmental influences on PBA or PBAD and how these may change over time.

We are aware of only two twin reports examining the heritability of PBA and PBAD; Cole's (Cole et al., 2017) cross-sectional analysis of 62 female twins at mean age 62 years, and Brouwer's (Brouwer et al., 2021) longitudinal analysis of 673 twins aged 10–23 years. The latter reported PBAD heritabilities up to 79% as well as longitudinal genetic correlations based on gray matter density and cortical thickness ranging 0.46–0.68. In addition to demonstrating heritability, these results suggest a combination of stable and age-varying genetic influences on brain aging at least in adolescents and young adults. Apart from Brouwer's analysis of adolescent and young adult twin data, to our knowledge, there have been no twin reports that have (i) estimated the genetic and environmental influences on PBA and PBAD on older populations, or (ii) tested developmental hypotheses regarding the stability of genetic influences on brain ageing. Given the emphasis on early detection of neurodegenerative diseases (Daviglus et al., 2010; Albert et al., 2011; Golde et al., 2011; Sperling et al., 2011a,b), we sought to address these gaps in our understanding.

Following the reports of Cole et al. (2017) and Brouwer et al. (2021) and based on published heritability estimates for cortical and subcortical volume (Baare et al., 2001; Wright et al., 2002; Peper et al., 2007; Kremen et al., 2010; Brouwer et al., 2014; Renteria et al., 2014; Satizabal et al., 2019), cortical thickness (Thompson et al., 2001; Kremen et al., 2010; Kremen et al., 2013a; Vuoksimaa et al., 2015), cortical surface area (Kremen et al., 2010; Eyler et al., 2011; Kremen et al., 2013a; Brouwer et al., 2014; Vuoksimaa et al., 2015), and diffusion MRI metrics (Elman et al., 2017; Gillespie et al., 2017; Hatton et al., 2018b), we hypothesized that MRI-based whole-brain indicators of PBA and PBAD should be heritable. Next, we tested developmental hypotheses. Theories of somatic mutation predict an accumulation of unrepaired cellular and molecular damage arising from genome instability during a single generation (Kirkwood, 1977; Morley, 1998; Kirkwood, 2005), which is consistent with autoregression (Guttman, 1954; Eaves et al., 1986; Boomsma and Molenaar, 1987; Boomsma et al., 1989). If changes in brain ageing do indeed stem from the accumulation of age-related genetic and environmental influences, the task is to determine how well autoregression explains observed PBA data. Alternatively, it is plausible that genetic and environmental influences in PBA are time-invariant and better explained by common or independent pathway theories (Neale and Cardon, 1992).

Our aim, therefore, was to explore the etiology of PBA (and PBAD) in a sample of middle- to later-age men with longitudinal MRI assessments. In addition to estimating PBA heritability, we tested competing hypotheses to explain best the longitudinal changes in genetic and environmental influences.

MATERIALS AND METHODS

Subjects

Participants comprise middle-aged male twins who underwent MRI scanning as part of the Vietnam Era Twin Study of Aging (VETSA) (Kremen et al., 2013b). Wave 1 took place between 2001 and 2007 (Kremen et al., 2006; mean age = 56.1, SD = 2.6, range = 51.1–60.2). Wave 2 occurred approximately 5.5 years later (mean age = 61.8, SD = 2.6, range = 56.0–65.9). Wave 3 occurred approximately 5.7 years later (mean age = 67.5, SD = 2.6, range = 61.4–71.7). All participants were concordant for US military service at some time between 1965 and 1975. Nearly 80% reported no combat experience. The sample is 88.3% non-Hispanic white, 5.3% African-American, 3.4% Hispanic, and 3.0% "other" participants. Based on data from the US National Center for Health Statistics, the sample is very similar to American men in their age range with respect to health and lifestyle characteristics (Schoeneborn and Heyman, 2009).

Ethics

Written informed consent was obtained from all participants. The University of California, San Diego, Human Research Protection Program Institutional Review Board approved the proposal to collect these data (Project #150572, 150537, 140361, 071446, 031639, and 151333). Data are publicly available through requests at the VETSA website.[1]

MRI Acquisition

A description of the MRI acquisition and derivation of the predicted brain age (PBA) and predicted brain age difference (PBAD) endophenotypes are provided in the Supplement. Discussed in detail elsewhere (Hatton et al., 2018a), PBA was estimated using the Brain-Age Regression Analysis and Computation Utility software BARACUS v0.9.4 (Github Inc, 2017; Liem et al., 2017). PBAD scores were calculated by subtracting PBA, also referred to as "stacked-anatomy" brain age

[1] http://www.vetsatwins.org

in BARACUS, from the chronological age. A negative PBAD is indicative of brain age estimated to be older than one's chronological age. Briefly, this approach works by relying on machine learning to estimate associations between imaging data and chronological age in training samples of varying age. We used the BIDS-mode docker on Ubuntu 16.04 using the default database that was trained on N = 1,166 subjects with no objective cognitive impairment (566 women/600 men, mean age 59.1 years, SD 15.2, range 20–80 years; Hatton et al., 2018a).

We note that while supervised machine learning algorithms such as BARACUS can detect informative multivariate patterns, the relative contributions of individual regions are not tested. Therefore, no inferences are made regarding particular regions of interest that might be responsible for individual differences in PBA or PBAD.

As noted in section "Subjects" there was considerable variation in chronological age at each wave and overlap in age ranges between the three assessments. Given the variation and overlap, longitudinal analysis of these wave-based data would therefore preclude any meaningful understanding of age-related changes. Ignoring irregular spacing between time intervals in longitudinal modeling can lead to biased parameter estimates (Estrada and Ferrer, 2019). Rather than employing definition variables to account for individual differences in age at assessment and irregular timer intervals (Mehta and Neale, 2005), our solution was to recode each subject's score according to their chronological age at assessment. Thus, for example, if two subjects "a" and "b" were both aged 60 at VETSA 1 and 2, respectively, each would be assigned a PBA score for age 60. Since each subject contributed a maximum of three data points between ages 51 and 72, this creates missing data for which Full Information Maximum Likelihood is well suited to handling. However, to reduce sparse data while maintaining computational efficiency, our "age-anchored" PBA and PBAD scores were re-coded to one of four age intervals according to each individual's age at assessment: 51–55; 56–60; 61–65; and 66–72 years.

There were 260, 251, and 126 subjects with PBA scores at one, two and three age intervals, respectively. Since there were only 3 VETSA assessments, no subjects had data from all four age intervals. Five participants were ascertained twice in the same 5-year age interval. Only their first observation was included. Prior to twin modeling all PBA and PBAD scores were residualized for the location and scanner differences (i.e., 1.5T vs 3T), age at assessment and ethnicity using the umx_residualize function in the umx software package (Bates et al., 2019), and given the range in birth year (1943–1955), residuals were also adjusted for cohort effects.

Statistical Analyses

The OpenMx$_{2.9.9.1}$ software package (Boker et al., 2011) in R$_{3.4.1}$ (R Development Core Team, 2018) was used to estimate correlations between the PBA scores and to fit univariate and multivariate genetic twin models (Neale and Cardon, 1992). The OpenMx code used for the multivariate analyses is included in the Supplement. Given the numbers of incomplete twin pairs (see **Supplementary Table 1**), methods such as Weighted Least Squares would result in significant listwise deletion thereby altering the accuracy of the PBA and PBAD means and variances. Fortunately, the raw data Full Information Maximum Likelihood (FIML) option in OpenMx$_{2.9.9.1}$ (Boker et al., 2011) has the advantage of not only being robust to violations of non-normality but also enables analysis of missing or incomplete data as well as the direct estimation of covariate effects. More accurate means and variance improve the estimation of the variances and covariance structure used to test our competing hypotheses.

Univariate Analyses

In univariate analyses, the total variation in each PBA score was decomposed into additive (A) heritability, shared or common environmental (C), and non-shared or unique (E) environmental variance components (see **Figure 1**). This approach is referred to as the "ACE" variance component model. The decomposition is achieved by exploiting the expected genetic and environmental correlations between MZ and DZ twin pairs; MZ twin pairs are genetically identical, whereas DZ twin pairs share, on average, half of their genes. Therefore, MZ and DZ twin pair correlations (r_A) for additive genetic effects are fixed to 1.0 and 0.5, respectively. The modeling assumes that shared environmental

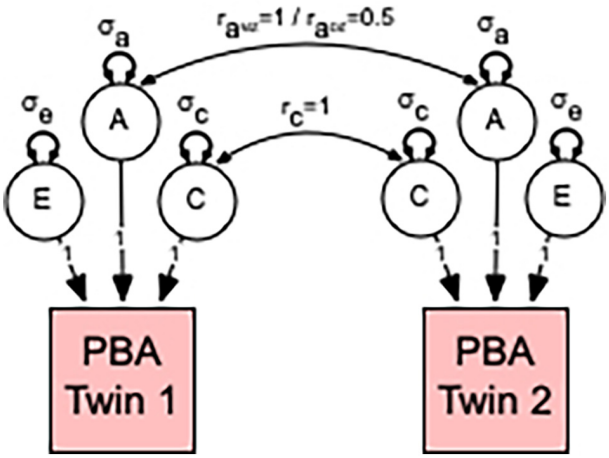

FIGURE 1 | Univariate model to estimate the relative contribution of genetic and environmental influences in predicted brain ageing (PBA). Individual differences in PBA are decomposed into three sources of variation: additive genetic (A); common or shared environmental influences (C); and unshared or random environmental influences as well as measurement error (E). This decomposition is achieved by specifying the expected genetic and environmental correlations between monozygotic (MZ) and dizygotic (DZ) twin pairs. MZ twin pairs are genetically identical, whereas DZ twin pairs share, on average, half of their genes. Therefore, the MZ and DZ twin pair correlations (r_{aMZ} and r_{aDZ}) for additive genetic effects are fixed to 1.0 and 0.5, respectively. This model also assumes that shared environmental effects are equally correlated (r_c = 1) in MZ and DZ twin pairs. Non-shared environmental influences are by definition uncorrelated within twin pairs (r_e = 0). Note that our method of estimating the relative contribution of genetic and environmental influences in PBA proceeds by estimating the additive genetic (σ_a), shared environmental (σ_c), and non-shared environmental (σ_e) variances for the A, C, and E latent factors. The size or contribution of these σ_e, σ_c, and σ_e variance components to the phenotype are assumed to be equal within twin pairs.

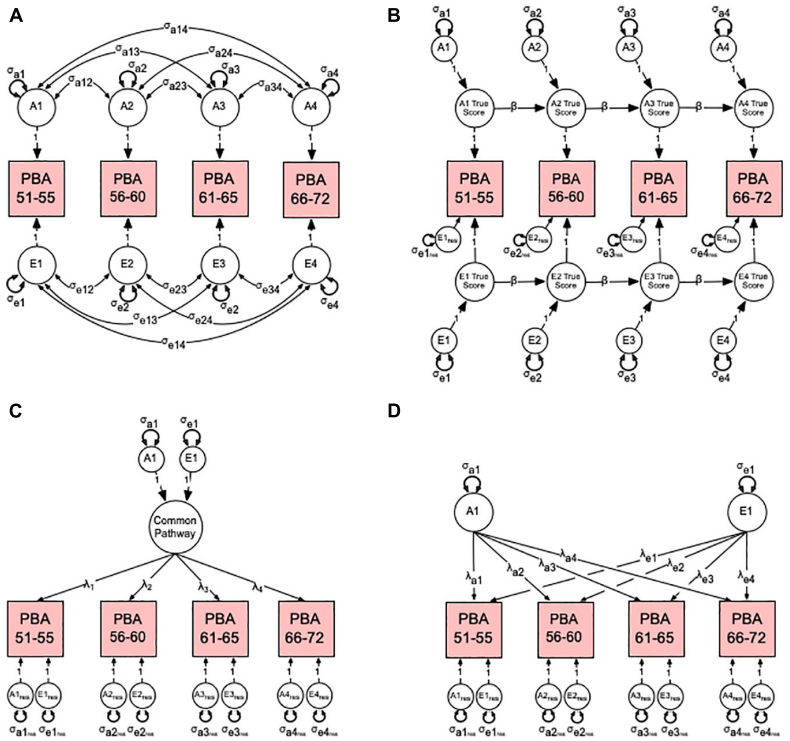

FIGURE 2 | Multivariate correlated factors **(A)** and competing hypothetical models to explain the sources of variance-covariance between the predicted brain age (PBA) scores. Competing models include **(B)** the auto-regression, **(C)** common pathway, and **(D)** independent pathway models. For brevity, only latent additive genetic (A1–4) and non-shared environmental (E1–4) factors are shown. **(A)** The multivariate correlated factor model estimates the size of the latent genetic and environmental variances and covariances (double-headed arrows). It is atheoretical and makes no prediction about the nature of change in PBA over time. **(B)** In the autoregression model, the time-specific genetic (σ_{a1-4}) and environmental (σ_{e1-4}) variance components or "innovations" for each genetic (A1–4) and environmental (E1–4) latent factor true score are estimated along with each variable's residual or error variance ($\sigma_{e1res-e4res}$). Also estimated are the autoregression or causal coefficients (β) from one latent true score to the next. **(C)** In the common pathway model, the genetic (σ_{a1}) and environmental (σ_{e1}) variance components for the common pathway, the factor loadings (λ_{1-4}), and latent genetic and environmental residuals ($\sigma_{a1res-a4res}$, $\sigma_{e1res-e4res}$) are estimated. **(D)** Finally, in the independent pathway model, genetic (σ_{a1}) and environmental (σ_{e1}) variance components are estimated independently with their factor loadings (λ_{a1-4}, λ_{e1-4}), and latent genetic and environmental residuals ($\sigma_{a1res-a4res}$, $\sigma_{e1res-e4res}$). See Supplement for more detailed modeling description.

effects (C) are equal in MZ and DZ twin pairs, whereas non-shared environmental effects (E) are by definition uncorrelated and include measurement error.

Multivariate Analyses to Test Competing Theories

This univariate method is easily extended to the multivariate case to estimate the size and significance of genetic and environmental influences within and between PBA over time.

In order to have a reference for contrasting and choosing the best fitting theoretical model, we first fitted a multivariate ACE "correlated factors" (**Figure 2A**) before fitted competing autoregression (**Figure 2B**), common (**Figure 2C**) and independent pathway (**Figure 2D**) models See Supplement for detailed modeling explanation. Given that (i) the machine learning method used here to calculate PBA and PBAD relied on a cognitively normal training sample and (ii) our twin analyses relied on a community-dwelling (non-clinically) ascertained sample, we therefore, refer to all A, C, and E variance components as genetic and environmental "influences", which assumes any observed variation in normal brain ageing comprises both risk and protective factors.

Model Fit

The best-fitting model was determined using a using a likelihood ratio test and the Akaike's Information Criterion (AIC) (27). For each best-fitting univariate and multivariate model, the parameters were then successively fixed to zero and their significance determined using a likelihood ratio chi-square test.

RESULTS

The numbers of complete and incomplete twin pairs by zygosity are shown in **Supplementary Table 1**. Descriptive statistics for each PBA score before and after residualization of the means and variances are shown in **Supplementary Table 2**.

Strength of Association

All phenotypic correlations between the PBA scores at each age interval were high and ranged from 0.67 to 0.76 (see **Table 1**).

TABLE 1 | Predicted brain age (PBA) phenotypic polyserial correlations.

	(1)	(2)	(3)	(4)
(1) PBA 51–55	1			
(2) PBA 56–60	0.67	1		
(3) PBA 61–65	0.76	0.74	1	
(4) PBA 66–72	0.67	0.72	0.75	1

Polyserial correlations represent the associations between the underlying liability rather than observed phenotypic distributions (Pearson, 1900; Pearson and Pearson, 1922).

Twin Pair Correlations

Table 2 shows the twin pair correlations by zygosity for the PBA scores at each age interval. If familial aggregation was entirely attributable to shared family environments, then monozygotic (MZ) and dizygotic (DZ) twin pair correlations would be statistically equal. In contrast, if familial aggregation was entirely attributable to shared additive (or non-additive) genetic factors, then DZ correlations would be 1/2 (or less) the size of the MZ twin pair correlations. Here, DZ twin pair correlations ranged from 0.1 to 0.6 and were ∼1/3 the size of the MZ twin pair correlations.

Univariate Analyses

Predicted brain ageing univariate model fitting results are shown **Supplementary Table 3**. At each age interval, the "AE" model with no common environmental effects provided the best fit. Familial aggregation in each PBA score could be entirely explained by additive genetic influences (A) ranging from 59 to 75% (see **Table 2**). All remaining variation was explained by non-shared environmental influences.

Multivariate Analyses

Both the autoregression and independent pathway models fitted the data poorly as judged by the significant change in their likelihood chi-squared ratios (see **Supplementary Table 4**). In contrast, the changes in the likelihood for the 1- and 2-factor common pathway models were not significant. Here, the 1-factor common pathway model provided a better comparative fit as judged by the lower AIC, and in subsequent modeling (see **Supplementary Table 5**), both the "CE" and "E" sub-models deteriorated significantly whereas the "AE" model yielded a non-significant likelihood ratio chi-square difference as well as the lowest AIC.

Thus, our multivariate analyses indicate that correlations between the PBA measures across time are best explained by a single factor, which can be explained 74% additive genetic and 26% non-shared environmental influences (see **Figure 3**). Total genetic variances (common and residual influences) in PBA at ages 51–55, 56–60, 61–65, and 66–72 were estimated to be 57, 69, 60, and 67%, respectively. For PBA at ages 61–65, the residual genetic variance was non-significant, indicating that genetic variance here is entirely captured by the common factor.

Genetic correlations between the four PBA scores were high and ranged from 0.78 to 0.92 (**Table 3**) indicating that the same genes are largely influencing PBA across time. In contrast, the environmental correlations were moderate to high, ranging from 0.45 to 0.58 (**Table 3**) suggesting that large proportions of the environmental influences are unique to each age interval.

We then applied the same univariate and multivariate modeling pipeline to the PBAD scores. All results are shown in the **Supplementary Tables 6–10**. Not only were the patterns of additive genetic and non-shared environmental factor correlations in the best fitting 1-factor common pathway "AE" model for PBAD nearly identical to PBA, the heritability of the common pathway was identical at 74%.

DISCUSSION

Individual differences in MRI-based estimates of PBA and PBAD are highly heritable, with genetic influences accounting for approximately three-quarters of the overall variance. The genetics of PBA are also highly correlated across time and these correlations can be best explained by a common set of heritable influences. Consequently, efforts to identify common molecular variants in PBA (Smith et al., 2020) may not require age-stratified samples. Our findings are also consistent with the hypothesis that common genetic influences explain most of the individual differences in brain ageing beginning in midlife and onward.

We also found that PBA could not be explained by shared environmental influences that drive twin pair similarity. Twins reared together are ideal controls for environmental influences that were shared during infancy and youth, continue to be shared, or continue to exert an impact. Naturally, as twins age and spend less time together, one would expect the number of directly shared environmental influences, relative to the time in their lives when they were reared together, to be diminished. Thus, in terms of individual differences in brain ageing, environments shared between family members that increase twin pair similarity, e.g., household and early rearing environments, parental income and SES (van der Loos et al., 2013; Davies et al., 2015), lack enduring or persistent effects and are of less importance than

TABLE 2 | Predicted brain age monozygotic and dizygotic twin pair polyserial correlations (corrMZ and CorrDZ) along with standardized variance components and 95% confidence intervals components for the best-fitting additive genetic (A) and non-shared environment (E) univariate models.

	$corr_{MZ}$	(95% CIs)	$Corr_{DZ}$	(95% CIs)	A	(95% CIs)	E	(95% CIs)
PBA 51–55	0.68	(0.53–0.78)	0.13	(−0.19 to 0.42)	0.64	(0.54–0.69)	0.36	(0.31–0.46)
PBA 56–60	0.70	(0.59–0.78)	0.29	(0.11–0.46)	0.71	(0.61–0.79)	0.29	(0.21–0.39)
PBA 61–65	0.60	(0.49–0.70)	0.20	(0.01–0.38)	0.58	(0.45–0.68)	0.42	(0.32–0.55)
PBA 66–72	0.66	(0.55–0.75)	0.18	(–0.07 to 0.58)	0.61	(0.47–0.71)	0.39	(0.29–0.53)

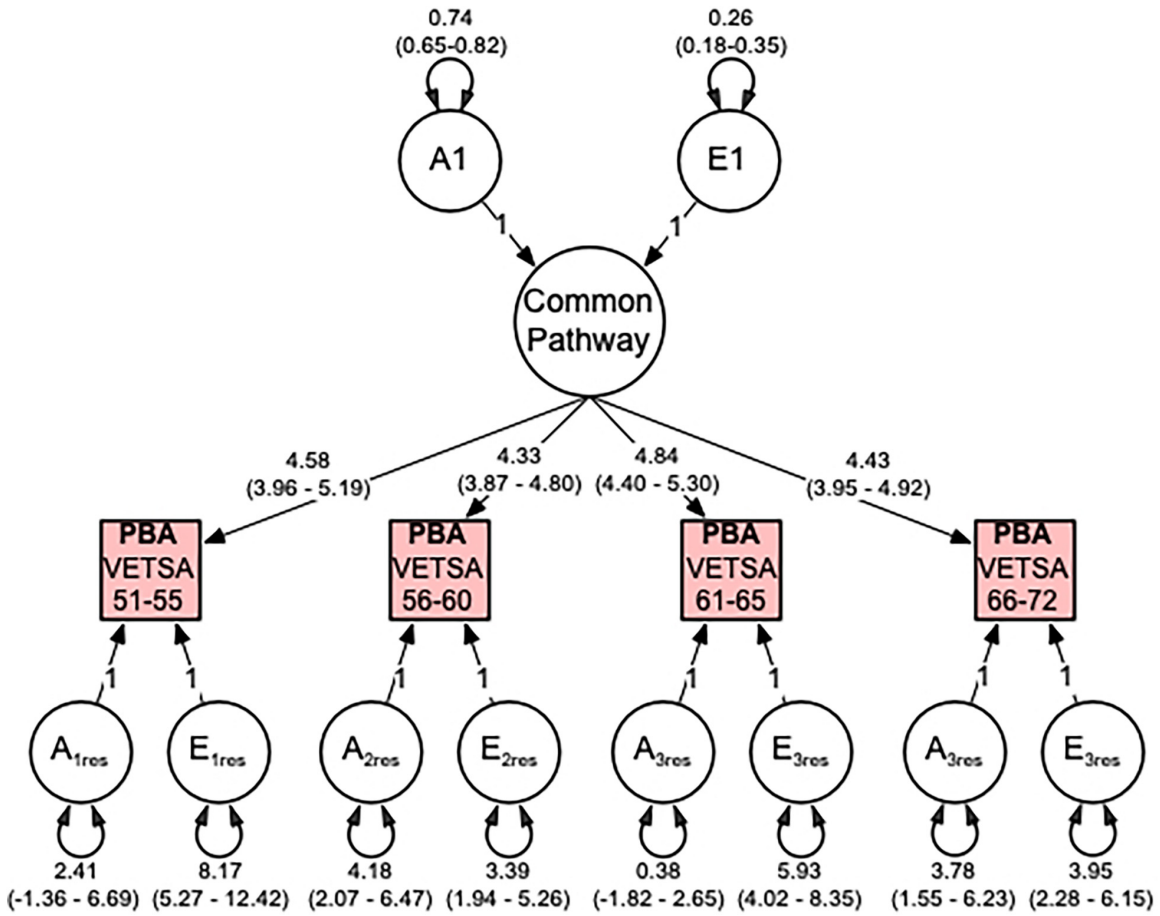

FIGURE 3 | Predicted brain age (PBA) best fitting common pathway (CP) multivariate model comprising additive genetic (A) and non-shared environment (E) variance components. Illustrated are the genetic and environmental variance components for the common pathway, the factor loadings from the CP to the observed PBA phenotypes, and the genetic and environmental residual variance components. All variance components are standardized and include 95% confidence intervals.

environments that are unique to individuals, e.g., diet, drug use or allostatic stressors such as negative life events (Hatton et al., 2018a). Indeed, we have previously shown that having more favorable and modifiable lifestyle behaviors such as a good diet, physical activity, social engagement, and less nicotine and alcohol consumption predict less advanced brain age and less AD-like brain aging (Franz et al., 2021; Whitsel et al., 2021). These findings may have implications concerning the efficacy of community-based versus individually targeted efforts to slow rates of brain ageing.

The hypothesis regarding accumulative environmental and molecular influences predicted by somatic mutation theories that ought to be captured by autoregression modeling was not supported. Instead, our data were consistent with what is perhaps a counterintuitive explanation. To the extent that any unrepaired damage is linked to genetic variation in our global indices of PBA, our modeling provided little support for autoregression features or accumulation of age-related or age-specific genetic influences over time. Likewise, we found no evidence to support the hypothesis that age-specific environmental influences are accumulative.

Instead, our best-fitting model suggests that brain ageing is best explained by stable genetic and environmental influences acting *via* a highly heritable common pathway accounting for most of the individual differences over a 21-year period. Our modeling makes no prediction regarding the number of genes likely involved in brain ageing. However, given recent genome wide association scan (GWAS) findings based on multiple brain ageing indices (Smith et al., 2020), including a GWAS of lifespan (Timmers et al., 2019), we speculate that ageing processes are highly polygenic. Our statistically derived common pathway should not be interpreted to represent any identifiable biological structure(s) governing this supervised learning index of ageing. It is, instead, consistent with Kirkwood's theory of a centrally regulated process of ageing, which under selection, has evolved to optimize the "allocation of metabolic resources across core processes like growth, reproduction, and maintenance" (Kirkwood, 2005). Kirkwood also argued that "network" theories of ageing used to describe multiple processes (Kirkwood, 1977, 2005) ought to distinguish upstream mechanisms that set ageing in motion from downstream mechanisms that affect ageing at the cellular level toward the end of life (Kowald and Kirkwood, 1996).

TABLE 3 | Predicted brain age additive genetic (below diagonal) and non-shared environmental correlations based on the best fitting "AE" 1-factor common pathway model.

	(1)	(2)	(3)	(4)
(1) PBA 51–55	1	0.48	0.45	0.47
(2) PBA 56–60	0.82	1	0.54	0.58
(3) PBA 61–65	0.92	0.87	1	0.53
(4) PBA 66–72	0.83	0.78	0.88	1

The high genetic correlation of $r_g = 0.72$ between ages 51–55 and 66–72 suggests, broadly, that genetic influences underpinning any putative "upstream" and "downstream" processes are mostly shared in common.

We have demonstrated that having more negative life events, particularly relating to interpersonal relationships, is associated with advanced PBA, i.e., higher predicted brain age relative to chronological age (Hatton et al., 2018a).

Limitations

Our results should be interpreted in the context of four potential limitations.

First, our hypothesis testing was not exhaustive. If PBA is related to rates of cellular or molecular ageing (Kirkwood, 2005), plausibly, genetic and environmental influences could unfold over time, and be better explained by growth processes (Nesselroade and Baltes, 1974; McArdle, 1986; McArdle and Epstein, 1987; Duncan and Duncan, 1991; Duncan et al., 1994). Although each twin pair was assessed on the same scanner on each measurement occasion, MRI data were collected on different scanners (i.e., 1.5T at VETSA 1 vs 3T at VETSA 2 and 3) resulting in likely measurement non-invariance across assessments. Consequently, data were residualized for these and other covariate effects. This resulted in the loss of interpretable mean and variance information necessary for latent growth curve modeling.

Second, our data were limited to midlife and early old age. Therefore, the stability in the genetic and environmental influences observed between ages 51 and 72 years may not generalize to other periods in the life course. For example, it is conceivable that genetic and environmental autoregression processes may have occurred before our first assessment (Elliott et al., 2019). There may also exist sub-groups of individuals for whom different autoregressions or hybrid auto-regression plus common factor models provide a better explanation of change over time. These hypotheses can only be resolved with additional data, e.g., data collected earlier in life, and are not within the scope of the current data.

Third, of the age at interview distribution at each of the VETSA waves spanned a decade. As mentioned in the "Materials and Methods", rather than employing definition variables to account for individual differences in age at assessment, our solution was to recode each subject's PBA and PBAD scores according to their chronological age at assessment. Our results should therefore, be interpreted as the average change of individuals with the 4-year age intervals. We did, however, repeat our analyses using the wave-based data whereby the assessment occasion was treated as a different time point (i.e., the VETSA interviews at waves 1, 2, and 3) while modeling age at assessment as a covariate. Here again, we found that the common pathway provided the best fit to the data.

Finally, our results may not generalize to women or ethnic minorities. We know of no other genetically informative twin studies with comparable and longitudinal MRI data. The uniqueness and size of our sample is a key strength of the VETSA cohort.

CONCLUSION

This is the first study to explore the genetic and environmental influences on PBA in a longitudinal sample. We assessed males age 51–72 years and report three major findings. First, measures of PBA were highly correlated across time. Second, the heritability estimates based on univariate twin analyses ranged from 59 to 74%. Finally, there was no evidence that PBA could be explained by an accumulation of age-specific genetic or environmental influences. Instead, genetic influences at each age interval were highly correlated and captured by a single, common factor with a heritability of 73%. Future analyses should explore the sources of genetic and environmental covariation between brain ageing and other complex behaviors related to cognitive decline.

DATA AVAILABILITY STATEMENT

OpenMx software coding used for the multivariate analyses is included in the **Supplementary Material**. All additional OpenMx software code is available upon request. Data are publicly available through requests at the VETSA website (http://www.vetsatwins.org).

ETHICS STATEMENT

The University of California, San Diego, Human Research Protection Program Institutional Review Board approved the proposal to collect these data (Project #150572, 150537, 140361, 071446, 031639, and 151333). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NAG, JAE, MSP, MJL, MCN, WSK, and CF were responsible for generating the hypotheses. SNH, DJH, AMD, JAE, CF-N, NW, MJL, WSK, and CF were responsible for data collection. NAG and MCN were responsible for the statistical analyses. NAG, SNH, DJH, AMD, JAE, LKM, LTE, CF-N, MWL, REM, OKP, XMT, HX, CAR, MSP, MJL, MCN, WSK, and CF were responsible for manuscript editing. All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by the National Institute on Aging at the National Institutes of Health grant numbers R01s AG050595, AG022381, AG037985; R25 AG043364, F31 AG064834, P01 AG055367, and AG062483. The funding sources had no role in the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

We would like to acknowledge the continued cooperation and participation of the members of the VET Registry and their families. The U.S. Department of Veterans Affairs, Department of Defense, National Personnel Records Center, National Archives and Records Administration, Internal Revenue Service, National Opinion Research Center, National Research Council, National Academy of Sciences, and the Institute for Survey Research, Temple University provided invaluable assistance in the conduct of the VET Registry. The Cooperative Studies Program of the U.S. Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.831002/full#supplementary-material

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Conflict of Interest: NAG hold equity in Cassava Sciences, Inc. LKM holds equity in CorTechs Labs, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 20 April 2022
doi: 10.3389/fnagi.2022.858405

Associations Between Age and Resting State Connectivity Are Partially Dependent Upon Cardiovascular Fitness

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OPEN ACCESS

Edited by:
Brock Kirwan, Brigham Young University, United States

Reviewed by:
Julie Suhr, Ohio University, United States
Jeffrey D. Johnson, University of Missouri, United States

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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *19 January 2022*
Accepted: *17 March 2022*
Published: *20 April 2022*

Citation:
Gust CJ, Moe EN, Seals DR, Banich MT, Andrews-Hanna JR, Hutchison KE and Bryan AD (2022) Associations Between Age and Resting State Connectivity Are Partially Dependent Upon Cardiovascular Fitness. Front. Aging Neurosci. 14:858405. doi: 10.3389/fnagi.2022.858405

Previous research suggests a marked impact of aging on structural and functional connectivity within the frontoparietal control network (FPCN) and default mode network (DMN). As aging is also associated with reductions in cardiovascular fitness, age-related network connectivity differences reported by past studies could be partially due to age-related declines in fitness. Here, we use data collected as part of a 16-week exercise intervention to explore relationships between fitness and functional connectivity. Young and older adults completed baseline assessments including cardiovascular fitness, health and functioning measures, and an fMRI session. Scan data were acquired on a Siemens 3T MRI scanner with a 32-channel head coil. Results from regression analyses indicated that average connectivity did not differ between young and older adults. However, individual ROI-to-ROI connectivity analyses indicated weaker functional correlations for older adults between specific regions in the FPCN and DMN and, critically, many of these differences were attenuated when fitness was accounted for. Taken together, findings suggest that fitness exerts regional rather than global effects on network connectivity.

Keywords: aging, fitness, functional connectivity, frontoparietal control network, default mode network

INTRODUCTION

Due to immense developments in medical technologies and treatments in recent decades, the oldest old (individuals 85+ years of age) have become the fastest growing segment of the U.S. population (National Institute on Aging and U.S. Department of Health and Human Services [DHHS], 2020). However, accompanying this enhanced longevity is an increase in the prevalence of conditions such as Alzheimer's Disease, osteoporosis, and cardiovascular disease, among others (Jaul and Barron, 2017). Even among relatively healthy adults, the normal aging process is characterized by declines in cognitive function, especially in the domain of executive functioning (EF), and changes to emotional and motivational processing (Scheibe and Carstensen, 2010; Murman, 2015). Such

changes often lead to decreased quality of life, as well as an increased susceptibility to fraud, scams, and financial distress due to impaired decision making (Denburg et al., 2007; Gamble et al., 2015).

With the utilization of functional neuroimaging techniques such as resting state functional connectivity magnetic resonance imaging (rs-fcMRI), alterations in functional coordination between brain regions, in the absence of a task, have become increasingly more apparent and robust across various populations (Zhang and Raichle, 2010). An examination of the current literature suggests at least two major resting state networks critical to executive, socioemotional, and economic functioning, namely the frontoparietal control network (FPCN) and the default mode network (DMN). The FPCN, which includes the dorsolateral prefrontal cortex (dLPFC), anterior prefrontal cortex, portions of the anterior cingulate (ACC), and dorsal precuneus, has been consistently implicated in general control processes across a wide variety of domains including socioemotional and neuroeconomic processes, as well as emotion regulation (Vincent et al., 2008; Depue et al., 2010; Ochsner et al., 2012), the selection and manipulation of information in working memory (Barnes et al., 2016), and processes related to the prioritization of information, especially under conditions of conflict (Zaki et al., 2010). Moreover, altered function of the dLPFC among clinical groups is associated with impulsive economic and risk-seeking behaviors (Meade et al., 2020).

The DMN generally comprises the medial prefrontal cortex (PFC), posterior cingulate cortex, and bilateral inferior parietal lobe, among other brain regions. It has been suggested to play an important role in introspective, self-generated processes (e.g., acting on internally generated information and evaluation of the self in reference to others) that may also influence socioemotional and neuroeconomic processes (Peters and Büchel, 2011; Andrews-Hanna, 2012). Of note, the FPCN and DMN often act in an anti-correlated manner to one another such that when individuals are engaged in cognitive control there is decreased activity in the DMN (Fox et al., 2005), although under conditions in which executive resources are needed to support internally directed cognition, these two systems may act in concert (Spreng et al., 2010).

In general, previous research suggests a marked impact of aging on structural and functional connectivity within each of these networks, but some discrepancies do exist. For example, some studies have found thickening of the ACC with age (e.g., Dotson et al., 2016) while other longitudinal analyses report significant thinning (e.g., Fjell et al., 2014). Similar discrepant results have been reported for regions of the DMN; notably, Salat et al. (2004) and Abe et al. (2008) both report age-related reductions in cortical gray matter in most anterior structures of the brain, though Salat et al. (2004) also found thickening of the medial orbitofrontal cortex with age. Findings for age-related alterations in functional connectivity are more consistent, with most studies reporting decreases in resting state connectivity within the FPCN (e.g., Geerligs et al., 2015) and DMN (e.g., Damoiseaux et al., 2008) among older adults relative to young adults (see also, review from Sala-Llonch et al., 2015). However, there are still discrepancies across studies with regard to the magnitude of age-related effects.

In a recent review paper, Andrews-Hanna et al. (2019) provide input on potential sources of variation in structural and functional connectivity findings by highlighting several challenges that often arise while conducting aging research. Broadly, they argue that previously reported age-related changes may be driven, to some degree, by motion/physiological, contextual, or motivational factors. For example, motion artifacts may partially account for discrepant results from structural studies, as older adults tend to show more variability in head motion during scanning (Savalia et al., 2017). Additionally, young and older adults may differ in their motivation for scanner-related tasks (e.g., staring at a fixation cross). Finally, though most connectivity studies exclude participants diagnosed with Alzheimer's disease, many fail to measure the associated risk factor of Mild Cognitive Impairment (Boyle et al., 2006). Thus, age-related changes reported by previous studies may be driven in part by the presence of undetected preclinical Alzheimer's disease in clinically normal adults.

However, it is also the case that aging is associated with reductions in physical activity (Sarkisian et al., 2005), voluntary exercise (Meisner et al., 2013), and cardiovascular fitness (Sandbakk et al., 2016). There is a growing body of research that suggests exercise in general (Li et al., 2017) and cardiovascular fitness in particular (Voss et al., 2016) have beneficial effects on brain function and connectivity. Much of this work has supported this relationship within older populations and in the domain of EF (Heyn et al., 2004). In the majority of studies comparing functional network connectivity in older vs. younger samples, the relative fitness/physical activity status of participants is not measured nor is there an explicit attempt to match participants on these variables. It is likely, however, that owing to general demographic trends the younger participants in these studies are both more active and more fit than the older participants. If true, it may be that the "age-related" network connectivity differences reported in previous studies have been overestimated and may be due—at least in part—to the effects of age-related exercise and fitness declines on connectivity rather than solely age.

The current analysis explores functional connectivity in core resting state networks strongly associated with cognition and EF in both young and older adults who were not currently meeting physical activity guidelines from the American College of Sports Medicine (American College of Sports Medicine [ACSM], 2014) at the time recruitment began for the study. The goals of this research are to replicate previous studies showing age-related differences in functional connectivity, specifically in the FPCN and DMN, and to investigate whether fitness may partially account for these differences in functional connectivity between young and older adults. Data were collected as part of a large-scale randomized controlled trial of a 16-week supervised exercise intervention designed to improve fitness, as well as cognitive, socioemotional, and economic function among sedentary adults 60 years of age and older. Given past research on age-related differences in functional and structural activity (reviewed in Sala-Llonch et al., 2015), we hypothesized that older adults would show decreased FPCN and DMN connectivity relative to young adults. Drawing from research on the neuroprotective effects of exercise (Colcombe et al., 2006), we further hypothesized that accounting for baseline fitness

should result in attenuated differences in functional connectivity between young and older adults.

MATERIALS AND METHODS

The fitness and neurocognitive function data herein were collected as part of a larger intervention to increase physical activity among older adults (NCT02068612; 5R01 AG043452-05) we called Fitness, Older Adults, and Resting State Connectivity Enhancement (FORCE). Briefly, the aims of the FORCE study were to characterize associations between fitness and various domains of functioning (e.g., cognitive, emotional), as well as to examine the effects of regular exercise participation on such associations. Older adults 60 years of age and older were recruited and completed extensive assessments including cardiovascular fitness (VO_2 peak), self-reported health and functioning measures, objective cognitive functioning measures, and a functional magnetic resonance imaging (fMRI) session. They were then randomly assigned to either low- or moderate-intensity exercise as part of a 16-week supervised exercise paradigm (results not reported here). A smaller group of young adults was recruited as a comparison for baseline fitness and neurocognitive function. These young adults completed all of the same baseline assessments but did not engage in the exercise intervention.

Participants

Participants were recruited through community advertisements, online resources such as Craigslist, ResearchMatch, outlets commonly frequented by adults of all ages, and public records from a marketing firm. To determine eligibility, interested individuals were asked to complete a phone screen. Inclusion criteria were: (1) 25–35 years of age for young adults or 60+ years of age for older adults; (2) sedentary, defined as fewer than 80 min per week of moderate-to-vigorous intensity exercise over the past 6 months; (3) completion of the Pfeiffer Short Portable Mental Status Questionnaire (PSPMSQ; Pfeiffer, 1975) with fewer than three errors; (4) willingness to be randomly assigned (older adults only); (5) able to safely engage in moderate-intensity exercise, as assessed by a study physician; (6) completion of a VO_2 max test without evidence of cardiac or other abnormalities; and (7) intending to remain in the Boulder-Denver area for at least 6 months (older adults only). Individuals with uncontrolled diabetes (hemoglobin A1C $>$ 7%), uncontrolled hypertension (systolic BP $\geq$ 160 mmHg and/or diastolic BP $\geq$ 100 mmHg), bipolar disorder, schizophrenia, dementia, Alzheimer's disease, MRI contraindications, and/or body size exceeding MRI capacity were deemed ineligible. Individuals who were pregnant or taking antipsychotic medications during screening were also excluded.

Procedure

All procedures were reviewed and approved by the University of Colorado Boulder Institutional Review Board. Written informed consent was obtained from all participants, after which each participant completed a baseline health and function assessment, medical and MRI screening, an interview about their current fitness level, a test of physical function, and a physician supervised treadmill familiarization activity with a 12-lead EKG. All data reported herein were collected prior to older adults being randomly assigned to exercise condition.

Magnetic Resonance Imaging Acquisition

Scan data were acquired on a Siemens 3T MRI scanner with a 32-channel head coil at the Intermountain Neuroimaging Consortium at the University of Colorado Boulder. Scan data acquired prior to April 2016 were collected on a TRIO system, while data acquired after April 2016 were collected on a Prisma Fit system. A scanner covariate was included in all analyses to control for differences in the scanner systems.

Each participant underwent a multi-echo magnetization prepared rapid acquisition with gradient echo (MPRAGE) T1 weighted anatomical scan (TR = 2,530 ms, TE = 1.64 ms, flip angle = 7°, FOV = 256 mm $\times$ 256 mm). A field map was acquired to reduce RF inhomogeneities and spatial distortion (TR = 400 ms, TE = 4.92 ms, FOV = 238 mm $\times$ 238 mm). A resting state M-EPI scan was also acquired (TR = 460 ms, TE = 29 ms, multiband acceleration factor = 8, slices = 48). During the resting state scan, participants were instructed to stare at a central fixation cross and relax for 8 min. Age-related movement artifacts were accounted for and corrected using a procedure similar to Power et al. (2012). Acquired images employed simultaneous image refocusing and multiband slice excitation (c.f., Feinberg et al., 2010). This newer method of spatial and temporal multiplexing has allowed for much faster sampling rates at $<$ 500 ms as compared to $\sim$2 s while still acquiring whole brain coverage. This acquisition method also has the effect of reducing high-frequency artifacts such as physiological noise, thereby increasing the signal-to-noise ratio by 60%.

Data Preprocessing and Analysis

Preprocessing was carried out through an SPM5-based automated analysis pipeline developed at the Mind Research Network (Bockholt et al., 2010), followed by the CONN Toolbox's[1] resting state functional connectivity preprocessing pipeline (Whitfield-Gabrieli and Nieto-Castanon, 2012). Preprocessing steps included removal of the first six frames to ensure intensity stabilization, skull stripping, motion realignment, segmentation of the structural image into gray matter, white matter, and cerebrospinal fluid, and identification of outlier frames, which were controlled for as first-level covariates using DVARS and framewise displacement (0.9 mm). Additional preprocessing included slice timing correction, adjustment for residual noise arising from white matter and cerebrospinal fluid, normalization of the structural image to MNI template, coregistration of the functional image to the segmented anatomical scan, and spatial smoothing (8 mm FWHM). Data were quality checked for gross artifacts or errors that may have occurred during preprocessing. Scans exhibiting excessive functional image distortion and/or magnetic field distortion were excluded (n = 4, all older adult participants).

[1] https://web.conn-toolbox.org/

TABLE 1 | Spherical regions of interest (ROIs) and their associated MNI coordinates.

Frontoparietal control network	
Lateral anterior prefrontal cortex	L: (–40, 50, 7); R: (40, 50, 7)
Intraparietal sulcus	L: (–43, –50, 46); R: (43, –50, 46)
Inferior temporal gyrus	L: (–57, –54, –9); R: (57, –54, –9)
Posterior-dorsal medial prefrontal cortex	L: (–5, 22, 47); R: (5, 22, 47)
Midcingulate	L: (–6, 4, 29); R: (6, 4, 29)
Posterior precuneus	L: (–4, –76, 45); R: (4, –76, 45)
Dorsolateral prefrontal cortex	L: (–45, 29, 32); R: (45, 29, 32)
Default mode network	
Medial prefrontal cortex	L: (–7, 49, 18); R: (7, 49, 18)
Posterior cingulate cortex	L: (–7, –52, 26); R: (7, –52, 26)
Posterior inferior parietal lobule	L: (–41, –60, 29); R: (41, –60, 29)
Superior temporal sulcus	L: (–64, –20, –9); R: (64, –20, –9)
Medial temporal lobe	L: (−25, –32, –18); R: (25, –32, –18)
Posterior-dorsal prefrontal cortex	L: (–27, 23, 48); R: (27, 23, 48)

L, left; R, right.

Seed based rs-fcMRI analyses were completed using the CONN Toolbox. Six-millimeter diameter spherical regions of interest (ROIs) were applied to the resting state data using MNI coordinates defined by Yeo et al. (2011) (see **Table 1**). A band pass filter was set to 0.009–0.08 Hz to remove low and high frequency components of the signal. Spurious artifacts from the subject-specific, white matter, and CSF segmentations were regressed out, as well as signal corresponding to physiological noise. The residual time course was despiked and a bivariate correlation with no weighting was applied and used for resting state functional connectivity ROI-to-ROI analysis. A Fisher r-to-z transform was then applied to aid in normality assumptions in the higher-level analysis.

Once the analysis was completed through CONN, the first-level connectivity Fisher transformed z-scores and each pair of ROIs within both networks were extracted for each participant. The scores were averaged across all pairs of ROIs for the FPCN and DMN, separately, yielding a single mean connectivity value for each participant for each network to be used in multivariate regression analysis in R. Second-level analyses were also performed in CONN to assess the effects of age (older adults = -1, young adults = +1) on within-network, ROI-to-ROI functional connectivity in both the FPCN and DMN. The CONN toolbox uses each ROI within a network as the seed and tests the group difference in its connection to each other ROI in the network (i.e., all possible pairwise connections in a network are tested). Those results that pass correction for false discovery rate (FDR) are then reported as significantly different between the two groups. The FDR approach is utilized to control for the increased Type I error associated with a large number of tests, as it controls for a low proportion of false positives. This was followed by an additional comparison of young vs. older participants that controlled for fitness (i.e., VO_2 peak). Both sets of results were analysis-level corrected and thresholded at p-FDR = 0.05.

Measures

To characterize the sample, participants self-reported their age, gender, race/ethnicity, education level, and socioeconomic status at baseline.

Two measures assessed self-reported exercise behavior. Days of moderate-to-vigorous physical activity over the past 7 days was measured with the Stanford 7-Day Physical Activity Recall (PAR; Blair et al., 1985). General exercise participation was assessed using the exercise subscale of the Community Health Activities Model Program for Seniors (CHAMPS; Stewart et al., 2001). In completing the CHAMPS, participants are asked to indicate how many total hours in a typical week they participated in each of the included activities. Example activities include "Work on your car, truck, lawn mower, or other machinery" and "Jog or run."

VO_2 peak was assessed using an incremental graded exercise test to exhaustion with breath-by-breath gas collection (MGC Diagnostics Ultima, Saint Paul, MN) on a motorized treadmill (Full Vision Inc., Trackmaster, Newton, KS). Treadmill speed throughout the test was determined using participant heart rate (HR) and ratings of perceived exertion (RPE; Borg, 1970). While VO_2 max is defined as "the highest rate of oxygen uptake and utilization by the body during intense, maximal exercise" (Cade et al., 2018), VO_2 peak is the highest value of VO_2 that an individual reaches on a specific test of high-intensity exercise. VO_2 peak was thus used as an objective measure of fitness, as it is not uncommon for sedentary individuals to become fatigued before reaching the VO_2 plateau requirements to measure VO_2 max. A modified Balke protocol was used (Balke, 1963). Initial treadmill speed was selected to elicit approximately 70% of age-predicted maximum HR and an RPE rating of 13 ("somewhat hard"; Borg, 1970). Once determined, speed remained constant throughout the test and grade was increased by 2% (or 2.5% for speeds 6 mph or greater) every 2 min until exhaustion. Heart rate was continuously monitored using a 12-lead electrocardiogram (ECG). VO_2 peak was calculated as the highest 30 s average during the test. Two participants unable to complete the VO_2 peak assessment on the treadmill due to orthopedic limitations and/or balance concerns completed the test on a cycle ergometer (Lode Excalibur, Groningen, Netherlands). The test began at a resistance of 0 watts and increased by 20–25 watts every 2 min until exhaustion.

RESULTS

Demographic Information

A total of 222 participants (42 young adults, 180 older adults) completed baseline measures of demographics, VO_2 peak, and functional connectivity. Most participants identified as White and approximately two-thirds were female. Compared with older adults, a significantly greater proportion of young adults reported having some college and a smaller proportion had an advanced degree. Additionally, far more older adults than young adults indicated a household income of > $60,000. VO_2 peak was significantly higher among young adults relative to older adults, as anticipated. Also as expected given our inclusion criteria, there were no significant differences in baseline exercise levels as assessed by the PAR and CHAMPS (see **Table 2**).

TABLE 2 | Baseline characteristics by age group; SES, socioeconomic status; PAR, days of moderate to vigorous physical activity on the Stanford 7-Day Physical Activity Recall; CHAMPS, Community Health Activities Model Program for Seniors.

		Young adults	Older adults	Equivalence test *p*-value
Gender	% Female	57.1	65.6	$p = 0.307$
Race	% White	69.0	93.3	$p < 0.001$
	% More than one race	16.7	1.1	
	% Asian	11.9	4.4	
	% Black	2.4	0.0	
Education	% High school diploma or less	2.4	3.9	$p = 0.069$
	% Some college	28.6	13.3	
	% Bachelor's degree	45.2	38.3	
	% Master's degree or higher	23.8	45.0	
SES	% < $30,000	61.9	17.2	$p < 0.001$
	% $30,000–$59,999	23.8	23.9	
	% > $60,000	9.5	56.7	
Age		28.86 (3.10)	67.41 (5.57)	$p < 0.001$
VO_2 Peak		35.96 (8.30)	24.93 (5.39)	$p < 0.001$
PAR		1.55 (1.90)	1.73 (1.95)	$p = 0.579$
CHAMPS		13.19 (6.49)	16.34 (10.05)	$p = 0.051$

For Age, VO_2 Peak, PAR, and CHAMPS, values are means and standard deviations are presented in parentheses.

Mean Within-Network Resting State Functional Connectivity Magnetic Resonance Imaging: Relationships With Age

Contrary to prior empirical studies, average FPCN connectivity did not differ between young (M = 0.26, SD = 0.08) and older adults (M = 0.24, SD = 0.07) [$t(220) = 0.905$, $p = 0.367$]. Likewise, average DMN connectivity did not differ between young (M = 0.35, SD = 0.11) and older adults (M = 0.34, SD = 0.11) [$t(220) = 0.512$, $p = 0.610$]. We next examined the association between within-network functional connectivity and continuously reported age within each group by regressing connectivity in both the FPCN and DMN on self-reported age in years.

Among young adults, age was not significantly associated with FPCN connectivity, $b = 0.003$, $t(40) = 0.703$, $\eta^2 = 0.012$, $p = 0.486$. In contrast, we observed a significant negative relationship between age and FPCN connectivity among older adults, $b = -0.002$, $t(178) = -2.199$, $\eta^2 = 0.026$, $p = 0.029$, such that as age increased, connectivity decreased (see **Figure 1A**).

Age and DMN connectivity were unrelated among young adults, $b = 0.004$, $t(40) = 0.794$, $\eta^2 = 0.016$, $p = 0.432$. Similarly, there was no relationship between age and DMN connectivity among older adults, $b = -0.002$, $t(178) = -1.221$, $\eta^2 = 0.008$, $p = 0.224$ (see **Figure 1B**).

Mean Within-Network Resting State Functional Connectivity Magnetic Resonance Imaging: Relationships With Fitness

To examine differences in functional connectivity by fitness, we estimated a series of models regressing FPCN and DMN connectivity on VO_2 peak in each age group separately.

Among young adults, the association between fitness and FPCN connectivity was marginal, $b = -0.002$, $t(40) = -1.692$, $\eta^2 = 0.067$, $p = 0.098$, such that as fitness increased, connectivity decreased. In contrast, there was no relationship between fitness and FPCN connectivity among older adults, $b = -0.001$, $t(178) = -0.768$, $\eta^2 = 0.003$, $p = 0.443$.

Fitness and DMN connectivity were unrelated among young adults, $b = -0.002$, $t(40) = -0.922$, $\eta^2 = 0.021$, $p = 0.362$. Likewise, fitness was not significantly associated with DMN connectivity among older adults, $b = 0.001$, $t(178) = 0.538$, $\eta^2 = 0.002$, $p = 0.591$.

Mean Within-Network Resting State Functional Connectivity Magnetic Resonance Imaging: Relationships With Age Controlling for Fitness

To examine differences in functional connectivity by age while controlling for fitness, we estimated a series of models regressing FPCN and DMN connectivity on age and VO_2 peak.

For young adults, as with the initial model, age was not a significant predictor of FPCN connectivity even after controlling for fitness, $b = 0.001$, $t(39) = 0.224$, $\eta^2 = 0.001$, $p = 0.824$. For older adults, and consistent with the initial analysis, there was still a significant relationship between age and FPCN connectivity, $b = -0.003$, $t(177) = -2.721$, $\eta^2 = 0.040$, $p < 0.01$, after controlling for fitness. However, note that for older adults, age was negatively correlated with fitness and average FPCN connectivity, but fitness and FPCN connectivity were unrelated (see **Table 3**). Given the co-linearity, this result should be interpreted with caution. Fitness was also a marginal predictor of FPCN connectivity, $b = -0.002$, $t(177) = -1.767$, $\eta^2 = 0.017$, $p = 0.079$, such that as VO_2 peak increased, connectivity decreased.

As with the initial analysis, age was not a significant predictor of DMN connectivity in either age group [younger: $b = 0.003$,

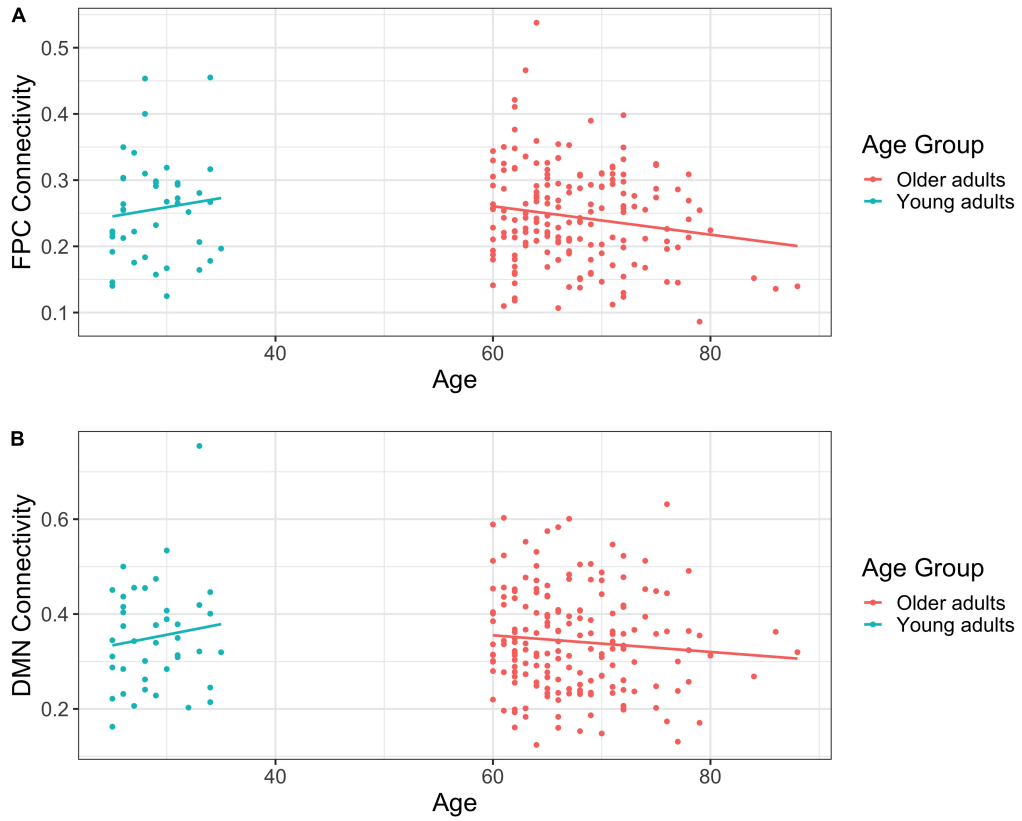

FIGURE 1 | (A) Scatterplot of frontoparietal control network (FPCN) connectivity by self-reported age in years. **(B)** Scatterplot of default mode network (DMN) connectivity by self-reported age in years.

TABLE 3 | Correlation matrix for study variables used in regression analyses; correlations in bold are significant at the $p < 0.05$ level; FPCN, frontoparietal control network; DMN, default mode network.

	Young adults				Older adults			
Variable	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1. Age	–				–			
2. VO_2 peak	–0.27	–			**–0.38**	–		
3. Average FPCN connectivity	0.23	–0.01	–		**–0.23**	–0.03	–	
4. Average DMN connectivity	0.10	–0.03	–0.03	–	0.01	–0.03	0.12	–

$t(39) = 0.540$, $\eta^2 = 0.007$, $p = 0.592$; older: $b = -0.002$, $t(177) = -1.095$, $\eta^2 = 0.007$, $p = 0.275$] even after controlling for fitness.

Pairwise Region of Interest-to-Region of Interest Resting State Functional Connectivity Magnetic Resonance Imaging

To look more specifically at functional connectivity across pairs of ROIs, rather than testing differences in "overall" levels of connectivity, we further explored these effects by assessing the strength of the relationship between specific ROIs within the FPCN and DMN.

Pairwise Region of Interest-to-Region of Interest Resting State Functional Connectivity Magnetic Resonance Imaging: Frontoparietal Control Network

Using the right inferior temporal gyrus as the seed region, there was stronger connectivity between the seed and the left posterior dorsal MPFC (*p-FDR* = 0.002), left intraparietal sulcus (*p-FDR* = 0.005), left midcingulate (*p-FDR* = 0.002), and right midcingulate (*p*-FDR = 0.010) among young adults relative to older adults. Similarly, when using the left midcingulate as the seed region, young adults displayed stronger connectivity between the seed and the left inferior temporal gyrus (*p*-FDR = 0.001). When using the right midcingulate as the seed region, there was stronger connectivity among young adults between the seed and the left inferior temporal gyrus (*p*-FDR = 0.001), left intraparietal sulcus (*p*-FDR = 0.031), left posterior dorsal MPFC (*p*-FDR = 0.031), and left lateral anterior PFC (*p*-FDR = 0.031) (see **Figure 2A**). When controlling for VO_2 peak, the age differences in connectivity between the left midcingulate seed region and the left inferior temporal gyrus, as well as between the right midcingulate seed region and the left posterior dorsal MPFC and left lateral anterior PFC, were no longer significant. However, correlations between the right

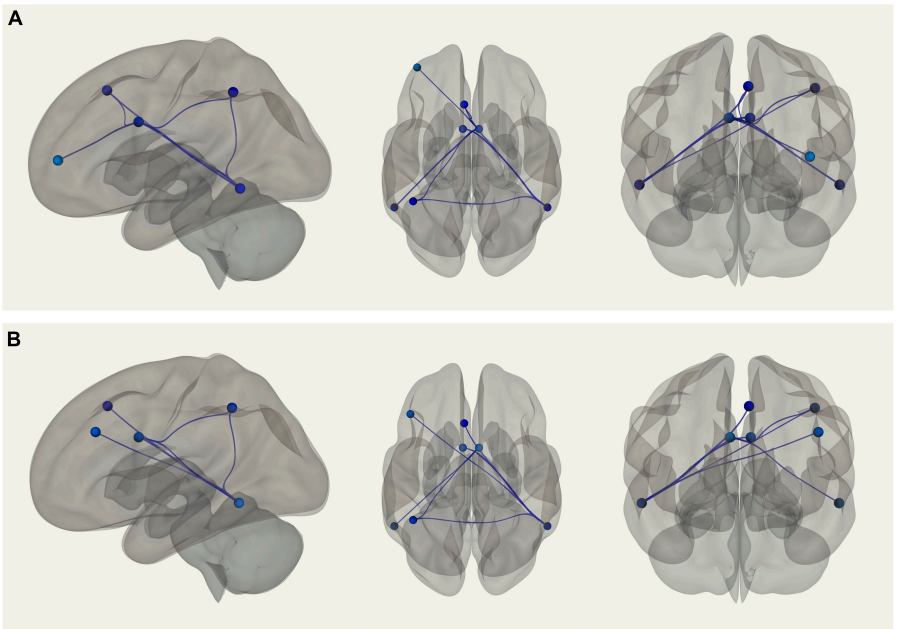

FIGURE 2 | (A) Sagittal, transverse, and coronal images displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults. Note that in this analysis there were no connections that were stronger in older adults. **(B)** Sagittal, transverse, and coronal images displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults. Note that in this analysis there were no connections that were stronger in older adults.

inferior temporal gyrus seed region and the left posterior dorsal MPFC, left intraparietal sulcus, left midcingulate, and right midcingulate were still significantly different between groups, such that connectivity was still stronger in younger adults. In addition, after controlling for VO_2 peak there was a new connection that was significantly stronger in younger adults between the right inferior temporal gyrus seed region and the left dLPFC. Correlations between the right midcingulate seed region and left inferior temporal gyrus and left intraparietal sulcus were also still significantly stronger in young adults (see **Figure 2B**). In sum, there were nine ROI-to-ROI connections, all involving the inferior temporal gyrus, the midcingulate, or both, that were significantly stronger in younger as opposed to older adults. After controlling for VO_2 peak three of those connections were no longer significantly different between the groups, while one new connection favoring younger adults emerged.

Pairwise Region of Interest-to-Region of Interest Resting State Functional Connectivity Magnetic Resonance Imaging: Default Mode Network

Using the right medial temporal lobe as the seed region, there was stronger connectivity between the seed and the left medial temporal lobe (p-FDR = 0.001) among young adults relative to older adults. Young adults also displayed stronger connectivity between the left and right superior temporal sulci (p-FDR = 0.006). Additionally, using the right superior temporal sulcus as the seed region, there was stronger connectivity between the seed and the right MPFC (p-FDR = 0.013) among young adults compared with older adults. In contrast, older adults displayed stronger connectivity between the left MPFC and right posterior dorsal PFC (p-FDR = 0.004) than young adults (see **Figure 3A**). When controlling for VO_2 peak, two of these four correlations were no longer significantly different between groups. Two correlations remained significantly different; stronger connectivity for older adults between the left MPFC and right posterior dorsal PFC and stronger connectivity for younger adults between left and right medial temporal lobe (see **Figure 3B**).

DISCUSSION

In the present investigation, we sought to replicate findings from previous studies reporting age-related differences in functional connectivity and associations between fitness and connectivity, and then determine whether age-related declines in fitness might partially account for observed age differences in connectivity. In regression analyses examining associations between age, fitness, and average functional connectivity, we found somewhat perplexing results. When comparing across age groups, average connectivity in both the FPCN and DMN did not differ between young and older adults. This result is inconsistent with past research (e.g., Andrews-Hanna et al., 2007). Interestingly, in the pairwise ROI-to-ROI rs-fcMRI analyses, the strength of many

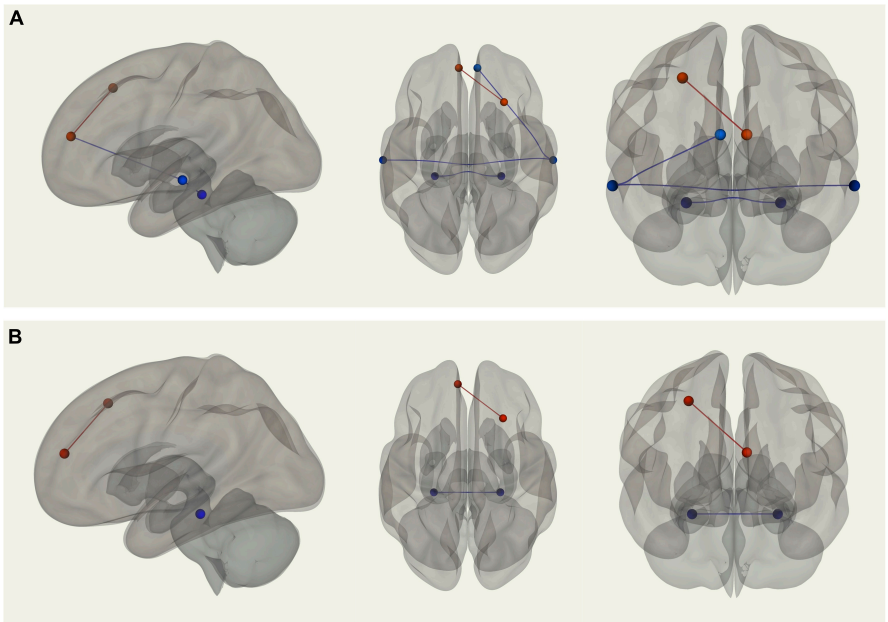

FIGURE 3 | (A) Sagittal, transverse, and coronal images displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults. **(B)** Sagittal, transverse, and coronal images displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults.

of the functional correlations between specific ROIs differed between young and older adults in this sample, with older adults generally exhibiting reduced connectivity. It is therefore possible that the observed weaker functional correlations between specific regions among older adults were "washed out" when examining average connectivity across nodes in a particular network.

In contrast to the group analyses, when age was treated continuously, we observed a significant negative relationship between age and FPCN connectivity among older adults. If fitness is indeed neuroprotective (Colcombe et al., 2006), we might expect this relationship to be weaker after accounting for fitness. Instead, though fitness shared a marginal negative association with FPCN connectivity, the effect of age remained significant (and even became a bit stronger). In fairness, this is likely a statistical suppression effect given the observed correlations between age and fitness (see **Table 3**). More specifically, among older adults, age was significantly negatively correlated with FPCN connectivity and fitness, but FPCN connectivity and fitness themselves were uncorrelated. This is clearly problematic, given that a potential covariate should have a statistical relationship with the outcome. It also further supports our previous conclusion, namely, that using a measure of average connectivity in the context of regression analyses may not be the best method to assess the effects of fitness on age-related differences in functional connectivity.

The individual ROI-to-ROI rs-fcMRI analyses were more consistent with findings from previous studies (e.g., Andrews-Hanna et al., 2007; Damoiseaux et al., 2008), indicating weaker functional correlations for older adults between several regions in both the FPCN and DMN. Furthermore, we found that, consistent with Voss et al. (2016) controlling for fitness generally resulted in some attenuation in the differences in functional connectivity in these particular ROI-to-ROI connections between the age groups. As one example to illustrate this point, the strength of the correlation between the right MPFC and the right superior temporal sulcus no longer differed between young and older adults once fitness was accounted for. This pattern held for other regions in the DMN, as well as for several functional correlations between regions in the FPCN. This suggests that "age-related" differences in network connectivity reported by previous studies may have been overestimated because many of those studies failed to control for the effects of fitness on connectivity. Bearing in mind that fitness was unrelated to *average* FPCN and DMN connectivity in both age groups, these findings also suggest that the effects of fitness on functional connectivity do not seem to be global. In other words, fitness can account for some of the age-related differences in functional correlations between specific brain regions, but it may not be useful for explaining age-related differences in average connectivity. Future work is needed to confirm these findings and to elucidate whether there is a consistent pattern to those connections that seem to be influenced by fitness changes and those that do not. It may also be fruitful to explore this global vs. specific distinction in the extent to which other factors, such as engagement in activities that are intellectually stimulating, might explain

differences in functional connectivity between young and older adults (Park et al., 2007).

Future research could also examine how connectivity *between* large-scale brain networks, in addition to alterations *within* large-scale networks, are related to both age and fitness. We primarily focused on within-network coupling in the FPCN and DMN given prior studies reporting sensitivity of those networks to age (reviewed in Sala-Llonch et al., 2015; Andrews-Hanna et al., 2019) and cardiorespiratory fitness (e.g., Voss et al., 2016), and in an attempt to reduce the number of overall statistical tests. However, older adults tend to show increased functional coupling between the FPCN and the DMN compared to young adults, as reflected in the Default-to-Executive Coupling hypothesis of aging (Turner and Spreng, 2015; Spreng and Turner, 2019). Since the FPCN is considered a brain-wide network "hub" that alters its coupling patterns with the DMN depending on one's current goals (Spreng et al., 2010), we reasoned that between-network in the absence of an explicit task at hand (i.e., "rest") might be especially sensitive to the co-occurring mental state of the participant, making findings difficult to interpret. Some participants may have viewed the "rest" period as an effortful externally oriented task (i.e., "remain focused on the fixation crosshair") whereas others may have viewed the rest period as an opportunity to advance their internally oriented goals (i.e., "use this time to plan the rest of my day"). Nevertheless, a more complete analysis of relationships between fitness and brain aging, and of the relation between resting state connectivity and ongoing thought patterns, would be of broad interest in future work.

As is always the case, some limitations need to be addressed. First, it is entirely possible that those participating in the FORCE study represent an especially healthy sample of older adults, in terms of both physiology and cognitive function. Participants were recruited from the Boulder-Denver area, two cities consistently cited as being among the healthiest and most active in the United States (Warren, 2020). In addition, our inclusion criteria required participants to be engaging in fewer than 80 min of moderate-to-vigorous exercise each week, rather than being completely sedentary. Thus, the older adults in our sample may have been healthier and fitter than what is typical. A related limitation is that most adults in the current sample reported being white, educated, and of middle socioeconomic status, further restricting the generalizability of the findings. The size of the young adult sample was also relatively small. Finally, our MRI scanner was upgraded part-way through the larger study, which past studies have shown can introduce bias and therefore reduce the integrity of the results (Chen et al., 2014). Efforts were made to reduce this bias by equating critical parameters across the systems and including a covariate for scanner in our analyses.

CONCLUSION

To conclude, this investigation employed a combination of analysis techniques to explore whether fitness partially accounts for important age-related differences in functional connectivity. Our initial approach involving a series of regressions using an average measure of connectivity showed that FPCN and DMN connectivity did not differ between young and older adults, and our measure of fitness was uncorrelated with average connectivity in both age groups. Seed-based rs-fcMRI analyses were more consistent with findings from previous studies (e.g., Andrews-Hanna et al., 2007), indicating weaker functional correlations between several regions in the FPCN and DMN among older adults as compared to younger adults. Critically, many of these differences were attenuated when fitness was accounted for. Taken together, our findings suggest that fitness exerts regional rather than global effects on network connectivity, which can account for some of the differences in functional connectivity across age.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Colorado Boulder Institutional Review Board, Office of Research Integrity. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DS, MB, JA-H, KH, and AB contributed to conception and design of the study. AB was responsible for funding acquisition and project administration. CG and EM performed the statistical analyses. CG, EM, and AB wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work was supported by the National Institute on Aging (5R01 AG043452-05, PI: AB).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.858405/full#supplementary-material

Supplementary Figure 1 | Sagittal image displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults.

Supplementary Figure 2 | Transverse image displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength

between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults.

Supplementary Figure 3 | Coronal image displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults.

Supplementary Figure 4 | Sagittal image displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults.

Supplementary Figure 5 | Transverse image displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults.

Supplementary Figure 6 | Coronal image displaying functional connections between ROIs within the FPCN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults.

Supplementary Figure 7 | Sagittal image displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults.

Supplementary Figure 8 | Transverse image displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults.

Supplementary Figure 9 | Coronal image displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults.

Supplementary Figure 10 | Sagittal image displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults.

Supplementary Figure 11 | Transverse image displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults.

Supplementary Figure 12 | Coronal image displaying functional connections between ROIs within the DMN that were significantly different in terms of strength between young and older adults when controlling for VO_2 peak and passed correction for false discovery rate; blue connections indicate stronger functional connectivity among young adults, while red connections indicate stronger functional connectivity among older adults.

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frontiers | Frontiers in Aging Neuroscience

REVIEW
published: 27 April 2022
doi: 10.3389/fnagi.2022.876159

Profiling the Research Landscape on Cognitive Aging: A Bibliometric Analysis and Network Visualization

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Objectives: This study aimed to profile the cognitive aging research landscape from 1956 to 2021.

Methods: A total of 3,779 documents were retrieved from the Scopus database for the bibliometric analysis and network visualization. By comparing each keyword's overall connection strength (centrality), frequency (density), and average year of publication (novelty) to the calculated median values acquired from the overlay view of the VOSviewer map, the enhanced strategic diagrams (ESDs) were constructed.

Results: The findings showed an increasing trend in the number of publications. The United States leads the contributing countries in cognitive aging research. The scientific productivity pattern obeyed Lotka's law. The most productive researcher was Deary, I. J., with the highest number of publications. The collaborative index showed an increasing trend from 1980 onwards. Frontiers in Aging Neuroscience is the most prestigious journal in the field of cognitive aging research. In Bradford core journals zone 1, the top 10 core journals of cognitive aging research provided more than half of the total articles (697, or 55.36 percent).

Conclusions: For the next decades, the trending topics in cognitive aging research include neuropsychological assessment, functional connectivity, human immunodeficiency virus (HIV), decision-making, gender, compensation, default mode network, learning and memory, brain-derived neurotrophic factor (BDNF), obesity, D-galactose, epigenetics, frailty, mortality, mini-mental state examination (MMSE), anxiety, and gait speed.

Keywords: cognition, aging, Harzing's publish or perish, BibliometriX R, VOSviewer, enhanced strategic diagram

OPEN ACCESS

Edited by:
Ian M. McDonough, University of Alabama, United States

Reviewed by:
Mani Abdul Karim, Periyar University, India
Hasley Rodrigo Pereira, Secretaria de Estado de Educação de Goiás, Brazil

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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *15 February 2022*
Accepted: *05 April 2022*
Published: *27 April 2022*

Citation:
Othman Z, Abdul Halim AS, Azman KF, Ahmad AH, Zakaria R, Sirajudeen KNS, Wijaya A and Ahmi A (2022) Profiling the Research Landscape on Cognition Aging: A Bibliometric Analysis and Network Visualization. Front. Aging Neurosci. 14:876159. doi: 10.3389/fnagi.2022.876159

BACKGROUND

The scientific literature has long demonstrated cognitive change as a natural part of aging. The dynamic and variable longitudinal changes in cognitive function that occur inherently during the aging process are referred to as cognitive aging (Harada et al., 2013). However, those who maintain their cognitive function at high levels, even with advancing age, are categorized as successful cognitive aging (Daffner, 2010).

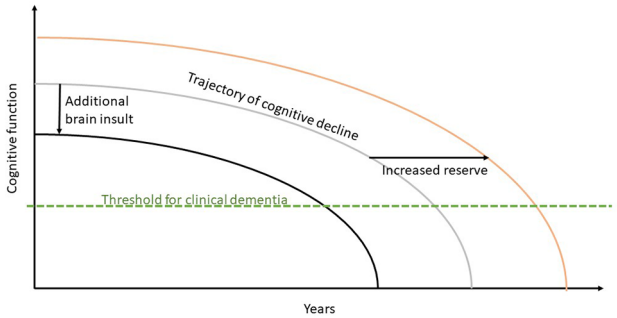

FIGURE 1 | Cognitive decline model. Figure adapted from Krivanek et al. (2021); copyright (2021) with permission from IOS Press.

The cascade model of cognitive aging suggested by Birren and Cunningham (1985) emphasized a life course approach to cognitive aging and cognitive performance. According to the model, primary aging is characterized by a steady deterioration in mental function, which is often accompanied by problems with memory (particularly new learning and retention), information processing, language, and other cognitive skills. Secondary aging refers to a loss of fluid and crystallized cognitive capacities caused by a disease process such as dementia, whereas tertiary aging refers to impairments in cognitive function caused by total biological devitalization of the organism before death (Birren and Cunningham, 1985).

Brayne and Calloway (1988), on the other hand, depict cognitive decline as a continuum, ranging from normal and successful aging to moderate cognitive impairment and dementia. This model depicts a general downward trend in all elements of cognitive ability, regardless of the competing danger of neuropathological alterations like dementia. However, Krivanek et al. (2021) suggested a new model of cognitive decline that depicts the progression of cognitive decline. In people with neurodegenerative diseases, this theoretical curve would shift to the left. On the other hand, boosting cognitive or brain reserve would shift this theoretical curve to the right, allowing patients to reach this threshold later in life (**Figure 1**).

Earlier neurocognitive models, which blend behavioral and neurological evidence to develop a conceptual model of cognitive aging, are based on neural compensation. These models, such as the Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002), the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH, Reuter-Lorenz and Cappell, 2008), the Posterior-Anterior Shift in Aging (PASA; Davis et al., 2008), and the Scaffolding Theory of Aging And Cognition (STAC and STAC-r; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014), postulate that older adults can perform as well as young adults on cognitive tasks depending on their capacity to recruit additional neural networks. These models, however, were unable to fully explain the cognitive deterioration that happens with healthy aging. Ebaid and Crewther (2020) then offered a theory of cognitive aging based on a system biology approach that combines the sensory deprivation hypothesis, the information degradation hypothesis, and the common-cause hypothesis. The theory stressed the significance of including all of the biological changes that frequently occur at a later age (Ebaid and Crewther, 2020).

Many studies on cognitive aging including its theories have been conducted in the past but only a few have kept track of the literature. The impact of literature on future research could be determined by bibliometric analysis, which is a quantitative analysis of publication metadata. The application of bibliometric approaches in the scientific and professional community has progressed much beyond the basic concept of simple lists of scientific production or citation indexing, and there is a wide range of applications across disciplines (Ellegaard, 2018). This is owing to advancements in bibliometric software such as VOSviewer, Gephi, and Leximencer, as well as the availability and accessibility of scientific databases like Web of Science and Scopus (Donthu et al., 2021).

Previous bibliometric studies have investigated general aspects of aging, namely, aging or oldest age or geriatric (Lund and Wang, 2020; Gonzalez-Alcaide et al., 2021), healthy aging (Gu et al., 2019), aging in combination with other issues such as reception by the scientific community (Glänzel and Schoepflin, 1995), physical therapy (Arnal-GÓmez et al., 2020), geriatric nursing (Ghamgosar et al., 2021), mobile technologies (Tajudeen et al., 2022), safety in-home care (Cao et al., 2021), subjective well-being (Dominko and Verbič, 2019), and specific to aging policies in China (Nan et al., 2020). This bibliometric analysis and network visualization, on the other hand, was carried out to explore the literature on cognitive aging in the Scopus database. It aimed to answer the following research questions:

1. How far has cognitive aging research progressed in terms of publication?
2. What is the scientific productivity pattern in the field of cognitive aging research?
3. Who are the most productive authors in the field of cognitive aging research?
4. What is the present state of collaboration in the field of cognitive aging research?
5. What is the pattern of research on cognitive aging that is scattered?
6. What are the main areas of cognitive aging research?

Therefore, in the present study, we attempted to reveal the publishing trends, scientific productivity patterns, the most productive authors, collaboration status, research patterns across the sources, and the major areas of cognitive aging research.

METHODS

Data Collection

This is a bibliometric study, which is a computer-assisted review procedure for identifying core research or authors, as well as their relationships by examining all publications related to a specific topic or field (De Bellis, 2009). The data for this study were retrieved and downloaded from the Scopus database on March 21, 2022. From 1956 to 2021, the search term "cogniti* AND ag*ing" in the article title was utilized. We included all the documents written in English from 1956 to 2021. We excluded

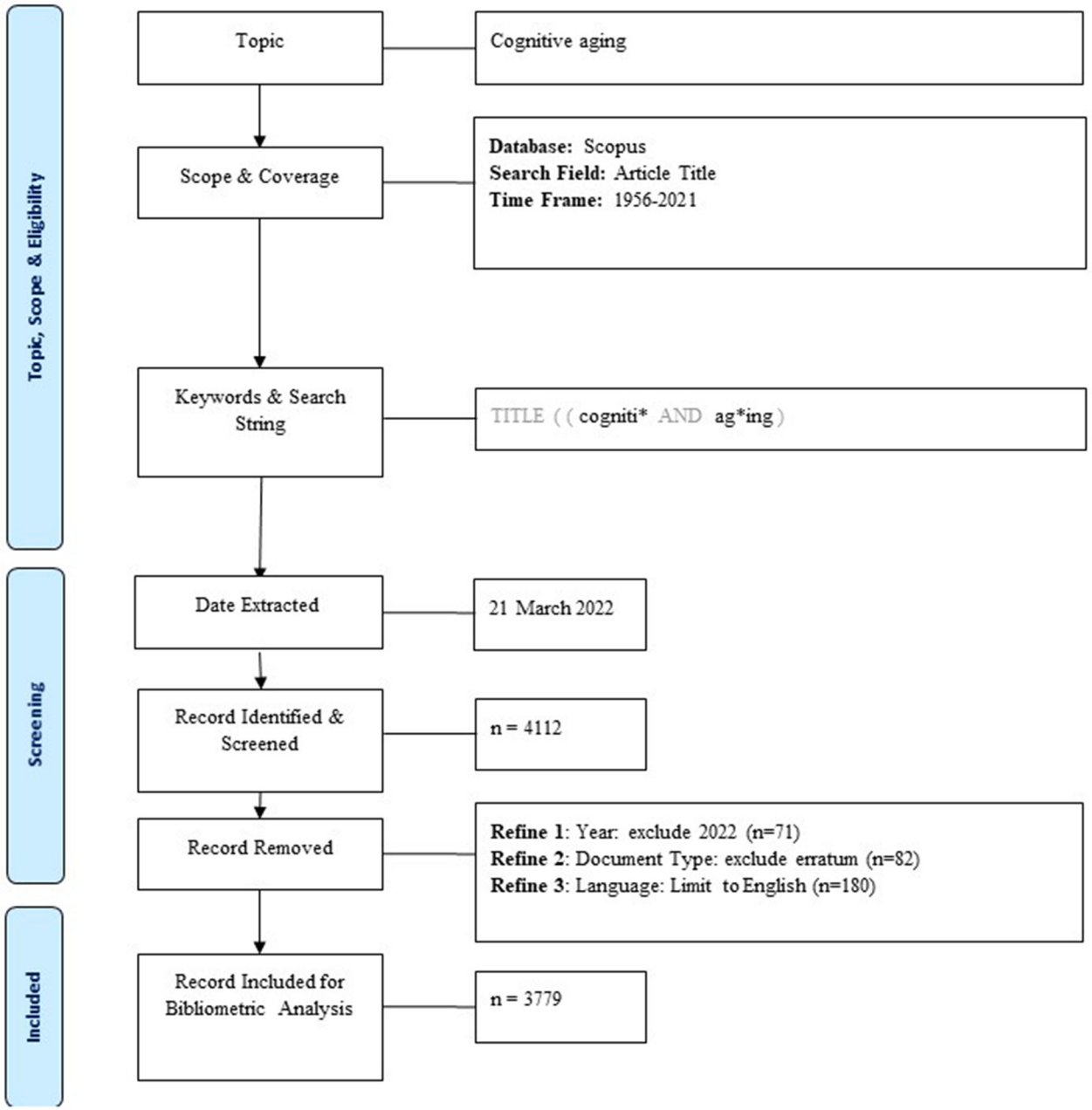

FIGURE 2 | PRISMA flow chart of data inclusion and exclusion (Page et al., 2021).

the 2022 documents (n = 71), since the 2022 data is incomplete, and the erratum (n = 82) to avoid double counting. Finally, 3,779 documents were identified and downloaded for further analysis (**Figure 2**).

Data Analysis

We have combined performance analysis and network analysis to answer our research objectives. The performance analysis, which includes citation- and publication-related metrics, was conducted using Harzing's Publish or Perish (Harzing, 2007) and BibliometriX R package software (Aria and Cuccurullo, 2017). The author's keywords were mapped using VOSviewer software (version 1.6.17), a popular tool with a simple graphic interface that can be used to create an author's keyword co-occurrence map (Van Eck and Waltman, 2021). It allows for identifying significant research subjects and finding large research clusters related to cognitive aging.

Based on a study by Feng et al. (2021), we have created the improved enhanced strategic diagram (ESDs) with the x-axis representing centrality, the y-axis representing density, and the

z-axis representing time on a three-dimensional plane. Centrality is a metric that measures the degree of interaction between networks (Cobo et al., 2011; Feng et al., 2021). A theme with a higher centrality score has more external connections to other themes (external strength) and hence has a bigger impact on the development and evolution of the research field (Cobo et al., 2011; Hansen et al., 2020; Feng et al., 2021). This study used the mean strength value of external links to other subjects, i.e., total link strength (TLS), to determine centrality. TLS values equal to or more than the calculated median value were regarded as high centrality, while those less than the median value were regarded as poor centrality.

The density of a topic, on the other hand, is used to determine the topic's internal strength or degree of interaction within a network (Cobo et al., 2011; Feng et al., 2021). The density of the author's keywords was determined in this study using co-occurrences. The median value was computed, and co-occurrence values equal to or higher than it was regarded as high density, while those below it were regarded as low density. The novelty of the study, on the other hand, is reflected by time (Feng et al., 2021), and the average publication year was employed in this study. In terms of novelty, the median value of the average publication year was determined, and average publication years equal to or greater than the median were regarded as novel and *vice versa*.

RESULTS

This study analyzed the main bibliometric indicators to profile the research landscape on cognitive aging from 1956 to 2021.

Publication and Citation Trend

There were 3,779 publications on cognitive aging retrieved from the Scopus database for this study. The first publication, "The judgment of ambiguous stimuli as an index of cognitive functioning in aging", was included in the analysis (Basowitz and Korchin, 1956). The number of publications related to cognitive aging remained in the single digits every year until 1987. The publication has been steadily expanding since then (**Figure 3**). Over the previous three decades, a rapid increase in publications has been reported (1991–2000: 236 or 6.22 percent; 2001–2010: 858 or 22.71 percent; 2011–2020: 2,247 or 59.48 percent). The trend line shows that the number of publications increases polynomially (R^2 = 0.9799), which is greater than a linear increase. In terms of citations, the overall number of citations per year showed a steady increase and an inverse correlation after 2011. The trend line shows that total citations increase polynomially (R^2 = 0.5417), indicating that citations are on an increasing trend, although in the last decade the increase has not been as high as in previous decades.

Geographical Distribution of the Publications

Table 1 shows the most productive countries based on the number of publications. The United States was the most prolific country and contributed almost half of the total publications. This was followed by the United Kingdom (n = 472 or 12.49%), Canada (n = 303 or 8.02%), Germany (n = 238 or 6.30%) and Australia (n = 219 or 5.80%). In terms of total citations, the United States had the lead in citations, followed by the United Kingdom, Canada, and Germany. However, France

FIGURE 3 | Total publications and citations on cognitive aging from 1956 to 2021.

TABLE 1 | Top 10 countries contributed to publications on cognitive aging.

Country	TP	TC	NCP	C/P	C/CP	*h*	*g*
United States	1,769	104,804	1,644	59.24	63.75	157	263
United Kingdom	472	24,650	435	52.22	56.67	72	143
Canada	303	18,871	277	62.28	68.13	67	132
Germany	238	11,947	219	50.20	54.55	58	103
Australia	219	8,432	205	38.50	41.13	48	83
China	206	4,608	175	22.37	26.33	37	60
Italy	173	5,062	157	29.26	32.24	38	66
France	158	10,963	144	69.39	76.13	37	103
Netherlands	154	7,439	149	48.31	49.93	49	83
Sweden	147	7,013	137	47.71	51.19	44	82

TP, total publication; TC, total citations; NCP, number of cited articles; C/P, citations per article; C/CP, citations per cited articles; h, h-index; g, g-index.

TABLE 2 | Number of publications on cognitive aging contributed by each author.

Number of publications	Number of authors	Percentage
1	9,880	76.4%
2	1,605	12.4%
3	607	4.7%
4	301	2.3%
5	140	1.1%
6	100	0.8%
7	72	0.6%
8	49	0.4%
9	29	0.2%
10	32	0.2%
>10	113	0.9%
Total	**12,928**	**100.00%**

(10,963) surpassed Australia (8,432), Italy (5,062), and China (4,608).

Scientific Productivity Pattern

A total of 12,928 authors contributed to the publications of cognitive aging research. **Table 2** lists the number of publications each author has contributed. The majority of the authors have only published once. Between 1956 and 2021, nearly a quarter of the authors contributed at least two articles on cognitive aging.

Most Productive Authors

The top 10 most productive authors are listed in **Table 3**. Based on the number of publications each had published, Deary, I.J., Petersen, R.C., and Brayne, C. were the three major contributing authors. However, Petersen, R.C. obtained the highest citations in terms of total citations, followed by Deary, I.J. and Brayne, C. The topmost cited article in cognitive aging co-authored by Petersen R.C. (Albert et al., 2011), may have contributed to this finding. H-index (Hirsch, 2005) is a measure of the broad impact of researchers' scientific achievement, especially in sciences and medicine. All the highly productive authors had a value above 20, except for Brodaty, H. and Sachdev, P.S.

Collaboration Status

The collaboration status of cognitive aging research was measured using the collaboration indices as listed in **Table 4**. Only one published article related to cognitive aging between 1956 and 1965 and the total publications started to increase in the mid-1980s onwards and this could be explained by the progress in cognitive aging research worldwide (Anderson and Craik, 2017). Only 405 or 10.72% were single-authored documents. The majority of the articles published between 1956 and 2021 had multi-authored documents, indicating collaboration. The co-authorship of four researchers on average (mean CI = 4.42) resulted in these multi-authored publications as shown by the collaboration index (**Figure 4**).

Scattering Pattern of Research Work Across the Sources

The distribution of document sources was assessed using Bradford (1950) to establish the scattering pattern of research on cognitive aging. The decreasingly ordered document sources were divided into three zones, each of which had an average number of 1,260 documents. **Table 5** shows that there were 32 Bradford's core journals (Zone 1 or nucleus) with 1,259 articles, Zone 2 had 187 journals (1,275 articles), and Zone 3 had 965 journals (1,245 articles).

Table 6 shows the top 10 core journals of cognitive aging research, which contributed more than half of the total articles (697 or 55.36%) in zone 1. In terms of total citations, Psychology and Aging obtained the highest total citations with two articles ranking among the top 10 most cited (Baltes and Lindenberger, 1997; Bialystok et al., 2004), followed by Neurobiology of Aging, Journals of Gerontology Series B Psychological Sciences and Social Sciences, Frontiers in Aging Neuroscience, and Journal of the American Geriatrics Society. Most of the journals listed in the top 10 core sources were specific to aging research except for PLoS One, which covers many subject areas.

Main Topics of the Research on Cognitive Aging

The main topics of cognitive aging research were identified using a keyword co-occurrence analysis. Only 113 of the 5,258 keywords used by the author surpassed the minimum occurrence level of 13 (**Figure 5**). Analytical (individual-based), descriptive (population-based), and experimental studies are the three clusters that emerge from the map (**Table 7**).

The ESDs were created by comparing each keyword's overall link strength (centrality), frequency (density), and average year of publication (novelty) to the derived median values obtained from the overlay view of the VOSviewer map. There are four different types of themes that can be determined based on the plane's position (Cobo et al., 2011; Feng et al., 2021). The four themes in

TABLE 3 | Top 10 authors contributed to publications on cognitive aging.

Author	TP	TC	NCP	C/P	C/CP	*h*	*g*
Deary, I.J.	66	3,761	64	56.98	58.77	33	61
Petersen, R.C.	53	9,989	48	188.47	208.10	27	53
Brayne, C.	51	3,693	49	72.41	75.37	31	51
Matthews, F.E.	42	3,082	40	73.38	77.05	25	42
Mielke, M.M.	40	1,405	38	35.13	36.97	22	37
Knopman, D.S.	39	2,467	37	63.26	66.68	24	39
Starr, J.M.	39	2,498	38	64.05	65.74	24	39
Brodaty, H.	34	1,198	30	35.24	39.93	18	34
Roberts, R.O.	31	2,295	30	74.03	76.50	23	31
Sachdev, P.S.	30	1,110	27	37.00	41.11	18	30

TP, total publication; TC, total citations; NCP, number of cited articles; C/P, citations per article; C/CP, citations per cited articles; h, h-index; g, g-index.

TABLE 4 | Collaboration indices.

Year	TP	TNA	SAP	%	MAP	%	TNA_{MAP}	CI
1956–1960	1	2	0	0.00	1	100.00	2	2
1961–1965	0	0	0	0.00	0	0.00	0	0
1966–1970	1	1	1	100.00	0	0.00	0	0
1971–1975	2	2	2	100.00	0	0.00	0	0
1976–1980	4	8	1	25.00	3	75.00	7	2.33
1981–1985*	12	27	1	8.33	9	75.00	26	2.89
1986–1990*	52	134	19	36.54	32	61.54	115	3.59
1991–1995*	90	253	20	22.22	64	71.11	233	3.64
1996–2000*	145	526	28	19.31	115	79.31	498	4.33
2001–2005	301	1,226	50	16.61	251	83.39	1,176	4.69
2006–2010*	557	2,650	91	16.34	465	83.48	2,559	5.50
2011–2015*	979	5,326	103	10.52	874	89.27	5,223	5.98
2016–2020*	1,269	8,212	71	5.59	1,196	94.25	8,141	6.81
2021	366	2,391	18	4.92	348	95.08	2,373	6.82

*TP, total publications; TNA, total number of authors; SAP, single author publications; MAP, multiple authors publications; TNA_{MAP}, total number of authors in MAP; CI, collaboration index = number of authors in the MAP/number of MAP. *1985—2 documents with 0 author; 1987—1 document with 0 author; 1994—2 documents with 0 author; 1995—4 documents with 0 author; 1997—1 document with 0 author; 1999—1 document with 0 author; 2006—1 document with 0 author; 2015—2 documents with 0 author; 2016—1 document with 0 author; 2019—1 document with 0 author.*

the novel publication year are depicted in **Figure 6A**. Emerging with high density (upper-left quadrant), emerging with low density (lower-left quadrant), core (upper-right quadrant), and interdisciplinary (lower-right quadrant) are the four categories (lower-right quadrant). **Figure 6B** depicts the four themes that existed in the old publication year: isolated (upper-left quadrant), obsolete (lower-left quadrant), mature (upper-right quadrant), and declining (lower-right quadrant).

DISCUSSION

The cognitive aging theory was first introduced by Welford and Birren in 1965 (Birren, 1965). Before 1965, cognitive aging research was descriptive, determining which areas of intellectual performance are impaired in older vs. younger persons (Anderson and Craik, 2017). Over the past three decades, the growing number of publications meant that research on cognitive aging was gaining traction around the world. This was in line with the findings on healthy aging and geriatric nursing research reported by Gu et al. (2019) and Ghamgosar et al. (2021), respectively. Furthermore, this continual increase in research has important clinical and intellectual implications, as it aids clinicians in better measuring, preventing, and treating cognitive aging by establishing individualized risk profiles connected to a personalized intervention strategy (Ryan et al., 2019). The total citations peaked in 2011, suggesting this to be the key year for the development of the field (Cao et al., 2021). Further investigation revealed that the National Institute on Aging-Association Alzheimer's working groups on Alzheimer's disease diagnostic criteria issued a set of recommendations for diagnosing mild cognitive impairment attributable to Alzheimer's disease in 2011 (Albert et al., 2011).

The United States was the most prolific country followed by the United Kingdom, Canada, Germany, and Australia. The productivity of the top five countries was in line with the recent study conducted by Arnal-GÓmez et al. (2020). The authors suggested that productivity was related to the aging of their population, as shown by the positive correlation between productivity and the aged population. However, in terms of scientific productivity pattern, as the number of publications contributed increased, the number of authors declined. This was consistent with Lotka's Law (Lotka, 1926), which stated that single-publication authors are far more likely to conduct subsequent research on similar research areas (Rowlands, 2005; Kushairi and Ahmi, 2021).

The collaboration index was on the rise, reflecting the growing complexity of multidisciplinary research and the increasing quantity and quality of the resultant publications

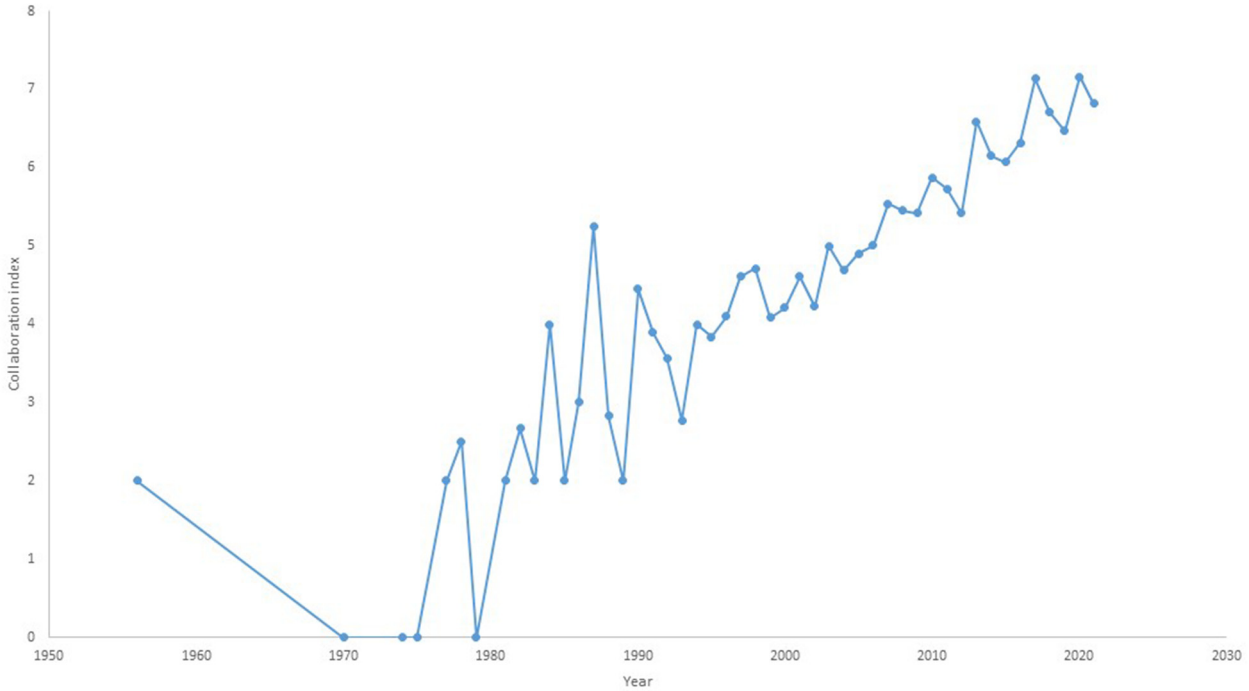

FIGURE 4 | Collaboration index each year from 1956 to 2021 in cognitive aging research.

TABLE 5 | Distribution of the sources and corresponding documents in three zones.

Zone	No. of sources	No. of articles	Percentage
1	32	1,259	33.32
2	187	1,275	33.74
3	965	1,245	32.94
Total	**1,184**	**3,779**	**100.00**

in cognitive aging (Stallings et al., 2013). According to several studies, research conducted by larger groups is more influential and impactful (Crane, 1972; Goffman and Warren, 1980). Furthermore, articles co-authored by international collaborators receive more citations than articles co-authored by domestic collaborators, implying that internationally co-authored articles represent a larger segment of global science (Narin et al., 1991). Dutt and Nikam (2015), however, reported that publications from certain prolific countries and institutions emerging from domestic collaboration resulted in a higher impact than those from international collaboration.

Based on the keyword co-occurrence analysis, there are three main clusters. In the analytical (individual-based) studies cluster, the main keywords were grouped into: (i) neuroimaging which includes various modalities; (ii) cognitive trajectories that are related to the major study groups; and (iii) cognitive domains that are related to the cognitive assessment frequently used (**Table 7**). The mature keywords are Alzheimer disease, mild cognitive impairment (MCI), magnetic resonance imaging (MRI), functional MRI (fMRI), and working memory, while the core keywords include cognitive aging, executive function, cognitive reserve, healthy aging, and diffusion tensor imaging

TABLE 6 | Top 10 core sources of the research on cognitive aging.

Source title	TP	TC	NCP	C/P	C/CP	*h*	*g*
Frontiers in Aging Neuroscience	111	2,992	105	26.95	28.50	30	50
Neurobiology of Aging	104	5,366	102	51.60	52.61	45	71
Journal of Alzheimer Disease	85	2,238	78	26.33	28.69	27	44
Psychology and Aging	82	7,633	80	93.09	95.41	45	82
Journals of Gerontology Series B Psychological Sciences and Social Sciences	69	3,303	62	47.87	53.27	28	57
Journals of Gerontology Series A Biological Sciences and Medical Sciences	54	2,806	51	51.96	55.02	29	52
Plos One	53	1,902	52	35.89	36.58	25	43
Aging Neuropsychology and Cognition	47	1,095	39	23.30	28.08	16	32
International Journal of Geriatric Psychiatry	46	1,413	44	30.72	32.11	19	37
Journal of the American Geriatrics Society	46	2,888	45	62.78	64.18	27	46

TP, total publication; TC, total citations; NCP, number of cited articles; C/P, citations per article; C/CP, citations per cited articles; h, h-index; g, g-index.

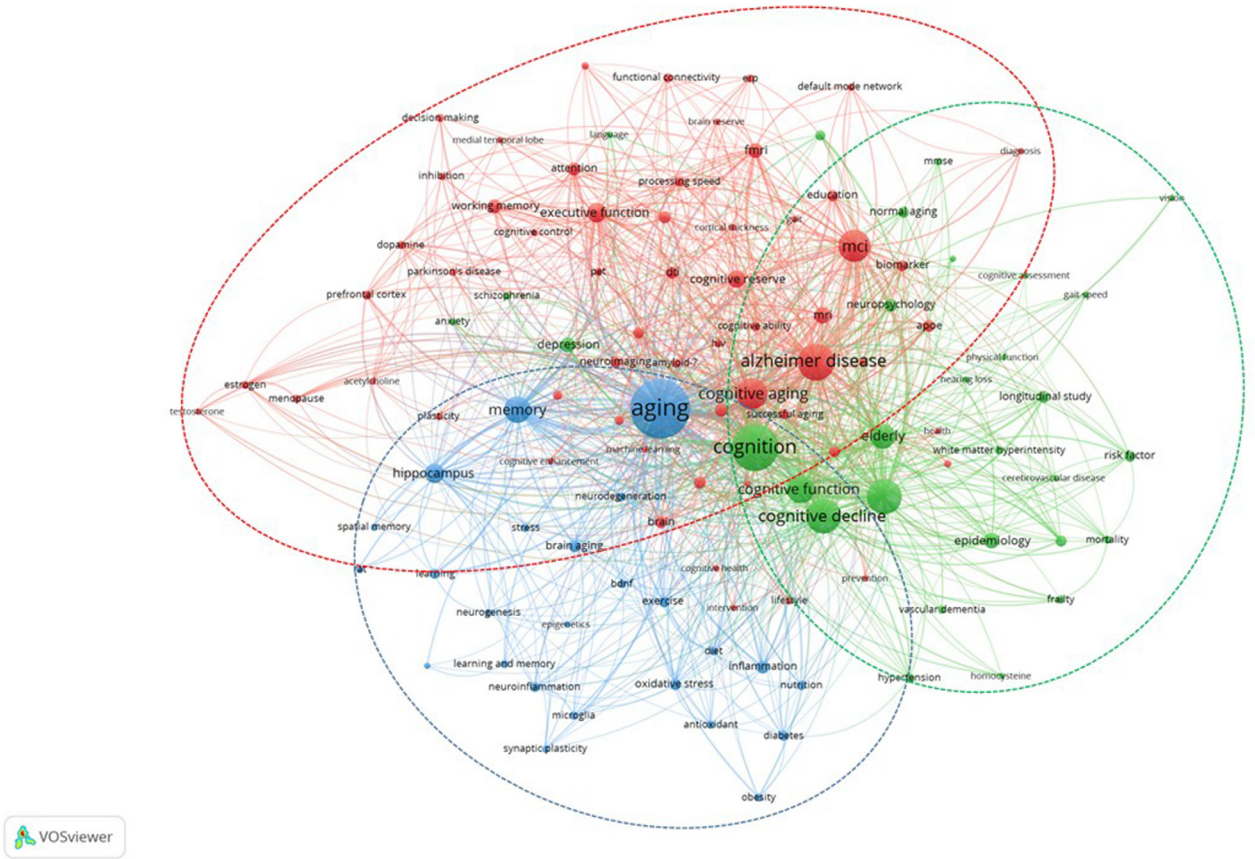

FIGURE 5 | The co-occurrence of the author's keywords minimum occurrence threshold of 13.

(DTI). These keywords highlight the main group of individuals, established neuroimaging, and cognitive domains related to analytical (individual-based) studies.

Individuals in the aging population vary greatly, and while some develop cognitive impairment (including mild cognitive impairment), Alzheimer's disease, and other types of dementia, others may retain their cognitive function to a major extent well into old age, which is also known as healthy aging (Nyberg et al., 2012). Reduced brain volume, cortical thinning, and deterioration in white matter microstructure are common age-related structural alterations (Fjell and Walhovd, 2010), which can contribute to lower cognitive performance in domains like executive function, memory, and processing speed (Nyberg et al., 2012; Grady et al., 2016; Cabeza et al., 2018). The cognitive reserve theory attempts to explain why some people can sustain cognitive performance while having a disease or aging-related brain abnormalities. Individuals with a larger cognitive reserve are thought to process information more efficiently, allowing them to functionally adapt to brain aging and sustain greater disease before cognitive deficits appear (Stern, 2002).

While the emerging keywords include functional connectivity, human immunodeficiency virus (HIV), decision making, gender, compensation, and default mode network, it is generally known that functional connectivity alterations associated with Alzheimer's disease start years before structural changes and clinical symptoms are noticed (Cieri and Esposito, 2018). In persons at risk of developing Alzheimer's disease, some resting-state fMRI studies have found increased functional connectivity between certain regions of the default network, while others have found decreased connectivity (Cieri and Esposito, 2018). Overactivation in functional connectivity across resting-state networks may be related to compensatory mechanisms even in cognitively preserved older adults, according to some studies (Li et al., 2015; Grady et al., 2016; Fjell et al., 2017). More advanced neuroimaging techniques with a higher spatial-temporal resolution, as well as methods to measure neurotransmitter activity or gene expression in real-time, may be developed, allowing for a better knowledge of the brain factors associated with cognitive aging and a new avenue for intervention (Anderson and Craik, 2017).

With a higher number of older individuals living with HIV in the era of antiretroviral therapy, there is a higher likelihood of cognitive decline, particularly in executive function, processing speed, vocabulary, recollection, and motor/psychomotor domains (Deng et al., 2021). In the available research, there is some evidence for premature and accelerated cognitive aging among HIV individuals, particularly in large and longitudinal studies and those with a higher number of older samples.

TABLE 7 | The main keywords in each cluster.

Cluster/Focus	Color	Keywords
1/Analytic studies (Individual-based)	Red	Neuroimaging: MRI, fMRI, DTI, PET. Cognitive trajectories: MCI, cognitive aging, healthy aging, successful aging. Cognitive domains: executive function, working memory, attention, episodic memory, processing speed, decision making, intelligence.
2/Descriptive studies (Population-based)	Green	Risk factors: elderly, depression, hypertension, schizophrenia, anxiety. Behavioural assessments: cognitive function, neuropsychology test, frailty, MMSE, language, gait speed, hearing loss, physical function, vision.
3/Experimental studies	Blue	Lifestyle: exercise, nutrition, antioxidant, diet. Animal/human models: diabetes, stress, obesity, D-galactose. Markers: oxidative stress, neuroinflammation, BDNF, microglia, neurogenesis, synaptic plasticity. Hippocampal functions: memory, learning.

MRI, magnetic resonance imaging; fMRI, functional MRI; DTI, diffusion tensor imaging; PET, positron emission tomography; MCI, mild cognitive impairment; MMSE, mini mental state examination; BDNF, brain-derived neurotrophic factor.

Future HIV and cognitive aging studies will need to standardize neuropsychological testing methodologies and outcomes, as well as use a large sample from collaborative multi-centers (Aung et al., 2021).

Decision-making deficit has been shown even in cognitively healthy older adults (Spreng et al., 2016; Bangma et al., 2017). It may increase vulnerability to fraud (Duke Han et al., 2016; Lamar et al., 2020), including financial exploitation. Weissberger et al. (2020) found that perceived financial exploitation in old age is linked to differences in whole-brain functional connectivity involving the hippocampus, insula, and medial frontal cortex, which is consistent with models linking age-related changes in decision-making and social cognition to financial exploitation.

There is still debate on the gender difference in cognitive performance with a particular interest in the older population. Previous studies have indicated that sex variations in cognitive performance remain until late adulthood (Siedlecki et al., 2019), as well as an unbalanced prevalence of neurodegenerative diseases associated with different cognitive impairments, for example, males are more likely to suffer from MCI and Parkinson's disease, while females are more likely to suffer from Alzheimer's disease (Cholerton et al., 2018; Sohn et al., 2018). Different interrelationships between cognitive functions could potentially explain sections of these different age-related trajectories, presenting a promising study topic.

Large-scale functional brain networks have also been used to investigate neurocognitive aging (Damoiseaux, 2017). Internally directed cognitive processes that rely on access to prior-knowledge representations to guide goal-directed behaviors generally engage the default network (Andrews-Hanna et al., 2014). During the performance of externally directed tasks, however, default-network are suppressed (Buckner et al., 2008). Reduced suppression, decreased within-network connectivity, and increased between-network connectivity are all age-related alterations in the default network, all of which are minimally controlled by task context (Spreng and Schacter, 2012; Rieck et al., 2017). These led to a default-executive coupling hypothesis of aging proposed by Spreng and Turner (2019). This hypothesis was based on findings that the lateral prefrontal cortex, responsible for executive function and cognitive control, is functionally coupled with engagement of the default network in old age.

In the descriptive (population-based) studies cluster, the main keywords were grouped into: (i) risk factors; and (ii) behavioral assessment. The mature keywords in this cluster include cognition, depression, neuropsychology, normal aging, and risk factor, while the core keywords were cognitive decline, dementia, cognitive function, elderly, and epidemiology. These

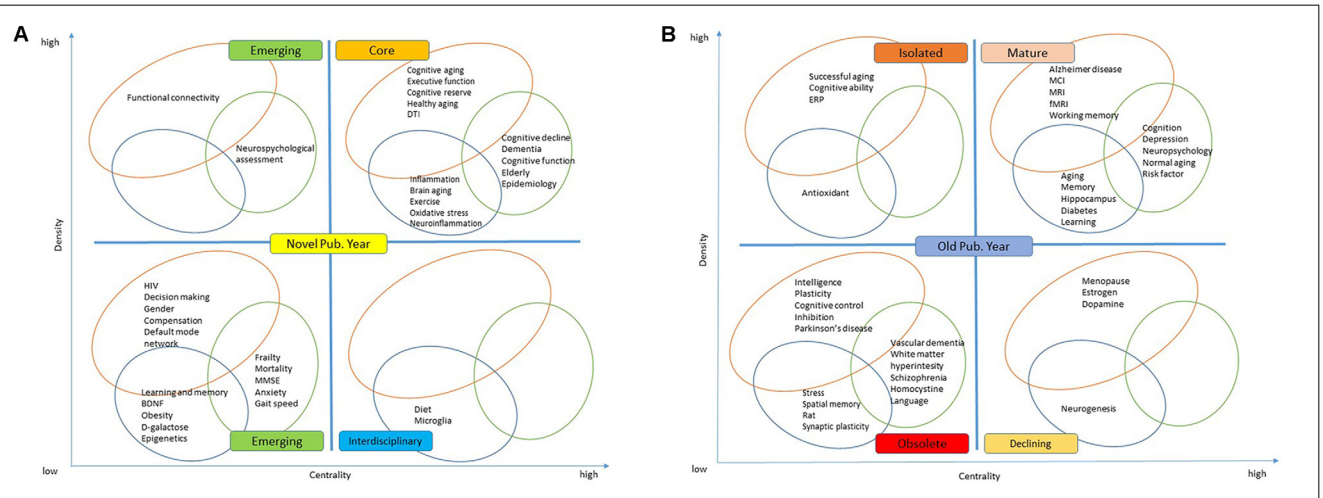

FIGURE 6 | Enhanced strategic diagrams showing **(A)** emerging, core, and interdisciplinary in the novel publication year **(B)** isolated, mature, obsolete, and declining topics in the old publication year.

keywords highlight the common types of population-based studies (epidemiology and longitudinal), established risk factors (elderly, depression, etc.), and behavioral assessments (cognitive function, frailty, mini-mental state examination (MMSE), etc.).

The emerging keywords in this cluster were neuropsychological assessment, frailty, mortality, MMSE, anxiety, and gait speed. These keywords reflect different behavioral assessments, frailty, gait speed, and MMSE, frequently used in population-based studies. The International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics defined cognitive frailty as comorbid physical frailty (>1 Fried criteria) and mild cognitive impairment (Petersen criteria; Kelaiditi et al., 2013; Rivan et al., 2020). Physical frailty such as gait speed and handgrip strength has been linked to cognitive decline in older persons in many previous studies (Demnitz et al., 2016; Kobayashi-Cuya et al., 2018; Chou et al., 2019). Furthermore, a recent theory has suggested a link between cognitive impairment, sensory deprivation, and common-cause hypotheses (Ebaid and Crewther, 2020).

In the experimental studies cluster, the main keywords were grouped into: lifestyle, animal/human models, cognitive markers, and hippocampal functions. The mature keywords in this cluster include aging, memory, hippocampus, diabetes, and learning, while the core keywords were inflammation, brain aging, exercise, oxidative stress, and neuroinflammation. This type of study normally assesses the role of lifestyle in affecting cognitive markers as well as hippocampal functions in animals and humans (Fordyce and Wehner, 1993; Vaynman et al., 2004; Gow et al., 2012; Woodard et al., 2012). The Cam-CAN data set provides a valuable resource that contributes to the expanding understanding of cognitive aging as a lifetime developmental process characterized by intricate interactions across life stages and cognitive domains. Thus, there is a need for large-scale cognitive aging experimental studies to include a wider range of ages and cognitive tasks (Shafto et al., 2020).

Learning and memory, brain-derived neurotrophic factor (BDNF), obesity, D-galactose, and epigenetics were among the emerging keywords in the experimental studies cluster. BDNF, a protein that regulates synaptic transmission and induces long-term changes in excitability and synaptic plasticity in the adult brain, has been shown to have a prominent role in neuron survival, growth, and function in experimental models (Miranda et al., 2019). The BDNF Val66Met polymorphism, which regulates BDNF expression, has been linked to resilience toward the effects of aging on cognition (Collins et al., 2021). In addition, epigenetics has been studied as a possible relationship between environmental/lifestyle factors (hormone status, food, stress, and exercise) and the variability of cognitive function as people age (Barter and Foster, 2018; Beydoun et al., 2020).

With a few exceptions, we have addressed all of the research objectives. To begin with, we only searched one database, Scopus, because it is the most comprehensive database (Zhu and Liu, 2020; Pranckute, 2021) and to avoid variations in data formats and field tags that would occur if we used data from multiple databases. Second, in order to prevent finding unnecessary documents, we run our search in the article title; nonetheless, we may overlook certain significant documents. Third, keyword cleaning and statistics are tailored to our specific needs, which may be limited by our professional knowledge and experience.

CONCLUSIONS

The United States continues to dominate in terms of publication and research collaboration in cognitive aging. The journals publishing themes relevant to aging research are the top sources of cognitive aging research. In the coming decades, the hot topics in cognitive aging research would be neuropsychological assessment, functional connectivity, HIV, decision-making, gender, compensation, default mode network, learning and memory, BDNF, obesity, D-galactose, epigenetics, frailty, mortality, MMSE, anxiety, and gait speed. These study findings provide useful references to health practitioners and researchers who are involved in cognitive aging management.

AUTHOR CONTRIBUTIONS

ZO and ASAH planned the study. RZ, KFA, and KNSS collected the data and drafted the manuscript. AHA, AW, and AA revised the manuscript and language. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
published: 03 May 2022
doi: 10.3389/fnagi.2022.854733

Machine Learning Decomposition of the Anatomy of Neuropsychological Deficit in Alzheimer's Disease and Mild Cognitive Impairment

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OPEN ACCESS

Edited by:
Annalena Venneri,
Brunel University London,
United Kingdom

Reviewed by:
Jiehui Jiang,
Shanghai University, China
Woon-Man Kung,
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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: 14 January 2022
Accepted: 22 March 2022
Published: 03 May 2022

Citation:
Dong N, Fu C, Li R, Zhang W, Liu M, Xiao W, Taylor HM, Nicholas PJ, Tanglay O, Young IM, Osipowicz KZ, Sughrue ME, Doyen SP and Li Y (2022) Machine Learning Decomposition of the Anatomy of Neuropsychological Deficit in Alzheimer's Disease and Mild Cognitive Impairment. Front. Aging Neurosci. 14:854733. doi: 10.3389/fnagi.2022.854733

Objective: Alzheimer's Disease (AD) is a progressive condition characterized by cognitive decline. AD is often preceded by mild cognitive impairment (MCI), though the diagnosis of both conditions remains a challenge. Early diagnosis of AD, and prediction of MCI progression require data-driven approaches to improve patient selection for treatment. We used a machine learning tool to predict performance in neuropsychological tests in AD and MCI based on functional connectivity using a whole-brain connectome, in an attempt to identify network substrates of cognitive deficits in AD.

Methods: Neuropsychological tests, baseline anatomical T1 magnetic resonance imaging (MRI), resting-state functional MRI, and diffusion weighted imaging scans were obtained from 149 MCI, and 85 AD patients; and 140 cognitively unimpaired geriatric participants. A novel machine learning tool, Hollow Tree Super (HoTS) was utilized to extract feature importance from each machine learning model to identify brain regions that were associated with deficit and absence of deficit for 11 neuropsychological tests.

Results: 11 models attained an area under the receiver operating curve (AUC-ROC) greater than 0.65, while five models had an AUC-ROC $\geq$ 0.7. 20 parcels of the Human Connectome Project Multimodal Parcelation Atlas matched to poor performance in at least two neuropsychological tests, while 14 parcels were associated with good performance in at least two tests. At a network level, most parcels predictive of both presence and absence of deficit were affiliated with the Central Executive Network, Default Mode Network, and the Sensorimotor Networks. Segregating predictors by the cognitive domain associated with each test revealed areas of coherent overlap

between cognitive domains, with the parcels providing possible markers to screen for cognitive impairment.

Conclusion: Approaches such as ours which incorporate whole-brain functional connectivity and harness feature importance in machine learning models may aid in identifying diagnostic and therapeutic targets in AD.

Keywords: cognitive impairment, neuropsychological tests, MRI, neural networks, machine learning, neuroimaging markers

INTRODUCTION

Alzheimer's Disease (AD) is the most common form of dementia, affecting millions worldwide (Prince et al., 2013). AD is characterized by the deposition of β-amyloid and tau protein, which often precede the onset of dementia symptoms by at least 10–20 years (Villemagne et al., 2013). AD initially progresses through a prodromal stage of mild cognitive impairment (MCI), defined as impairment in any single cognitive domain (Vega and Newhouse, 2014). Patients with MCI may also progress to other types of dementia, remain stable, or return to a cognitively unimpaired state (Giorgio et al., 2020). There is therefore a need to disentangle higher cognitive functioning in the neurodegenerative disease states and examine overlaps and differences to provide insight into both pathological and normal age-related neurocognitive functioning. This will in turn improve diagnostic and therapeutic approaches.

Currently the diagnosis of MCI and AD is based on clinical evaluation, while structural changes are often not detected in early disease, even when imaging is interpreted by experienced radiologists. Due to the advancement of machine learning algorithms and new data, we have the opportunity to analyze large data sets and build prediction models to inform clinical practice (Panch et al., 2018; Davenport and Kalakota, 2019). Various studies have utilized machine learning to predict the conversion of MCI to AD based on neuropsychological measures and clinical markers, with several studies focusing on neuroimaging models (Huang et al., 2020; Stamate et al., 2020; Syaifullah et al., 2020; Grueso and Viejo-Sobera, 2021). Wee et al. (2012) employed support vector machines to demonstrate that a multimodal approach combining functional and structural connectivity data improved the accuracy of MCI classification. Shi and Liu extracted features from resting-state functional magnetic resonance imaging (rsfMRI) to classify stages of MCI (Shi and Liu, 2020). Syaifullah et al. (2020) developed a technique combining SVM with voxel-based morphometry and MMSE scores which substantially outperformed radiologists in diagnosing AD. Jitsuishi and Yamaguchi investigated multiple types of modalities to demonstrate that diffusion parameters was most accurate in distinguishing early and late MCI (Jitsuishi and Yamaguchi, 2022). In contrast, most of the existing literature preselects features to focus the machine learning model's classification. While this results in high diagnostic accuracy, potentially crucial information about the disease process may be discarded. In the case of resting state functional connectivity, several studies have demonstrated key changes in brain network architecture across several large-scale networks, including the default mode, salience and limbic networks (Prasad et al., 2013; Badhwar et al., 2017; Ye et al., 2019). Many of these changes are can also be seen up to 4 years before the symptomatic onset of AD (Wisch et al., 2020). Since these large-scale functional networks comprising the seven-network model detailed by Yeo et al. (2011) are responsible for the complex processes underlying cognition (Yeo et al., 2011), it is important to formulate a network-based model of cognition in AD. This feat is, however, complicated by the magnitude of the data, which requires sophisticated machine learning tools to both make predictions, but also identify clinically meaningful targets for treatment. Therefore, models incorporating whole-brain functional connectivity and employing a network-based analysis may provide actionable insight and guide symptom-specific therapies.

In this study, we performed functional connectivity-based analysis and utilized a recently described machine learning approach (Doyen et al., 2021) to identify commonalities and differences in brain regions across neuropsychological domains in a cohort of MCI and AD patients, and age-matched cognitively unimpaired subjects. We sought to explore patterns among these regions to identify potential markers which may be used in future studies to develop better disease classifiers. We believe our methods will provide a basis for the utility of functional connectivity in improving diagnosis and patient selection for treatment in MCI and AD.

MATERIALS AND METHODS

Patient Cohort

Participants were recruited from the Department of Neurology and Memory Clinic in Shanghai Tongji Hospital between September 2017 and January 2021. All participants were Chinese, right-handed, and between 50 and 85 years old. The participants were divided into three groups: AD group, MCI and control group.

Exclusion criteria included: (1) definite history of stroke; (2) definite history of other diseases of the central nervous system such as infection, demyelinating diseases, and Parkinson's disease; (3) definite history of mental illness such as schizophrenia, major depressive disorder; (4) serious physical disease; (5) alcohol or drug addiction; (6) unable to cooperate with neuropsychological tests; (7) MRI contraindication; (8) iodine allergy.

Subjects included in the AD group had to meet the clinical diagnostic criteria set out by the National Institute on Aging and the Alzheimer's Association (NIA-AA) (Albert et al., 2011). Inclusion in the MCI group was based on the neuropsychological Jak/Bondi criteria (Bondi et al., 2014) and the Petersen/Winblad criteria as operationalized by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Marder, 2005). Specifically, the criteria included (a) the subject and their caregiver had complaint of memory/cognitive decline; (b) Mini-Mental State Examination (MMSE) MMSE or MoCA-B scores met the following criteria adjusted by education: MMSE $\leq$ 24 for Junior high school or above, or MMSE $\leq$ 20 for primary school, or MMSE $\leq$ 17 for illiteracy; or MoCA-B $\leq$ 24 for Bachelor degree or above, or MoCA-B $\leq$ 22 for middle school, or MoCA-B $\leq$ 19 for primary school or below; (c) Clinical Dementia Rating Scale (CDR) of 0.5; (d) met any of the following three criteria: (1) at least two performances within a cognitive domain fell below the established cutoff (> 1SD); (2) at least two cognitive domains were impaired (> 1SD); (3) had more than one function described in instrumental activities of daily living (IADL-14) scale scored 0 point.

All participants provided informed consent. This study was reviewed and approved by the Institutional Review Board at Tongji University.

Neuropsychological Testing

All participants underwent a comprehensive Neuropsychological Test Battery (NTB) that included the MMSE, MoCA-B, tCDR, IADL-14, and the Hachinski Ischemic Score (HIS). Memory function was assessed by the Hopkins Verbal Learning Test-Revised (HVLT-R, including immediate recall test, the 5-min delayed recall, the 20-min delayed recall test), and the logical memory test (Wechsler memory scale). Language function was measured by the Verbal Fluency test and the Boston Naming Test (BNT; the 30-item version). Executive function was assessed using the Shape Trail Test-A and B (STT-A, STT-B). The larger scores in STT-A or STT-B test indicates longer time to complete the task and poorer executive performance. Visual space navigation function was measured by the Rey-Osterrieth Complex Figure Test (CFT, including the copy test and the recall test). The assessments were performed by a neurology clinician qualified in neuropsychological assessment.

Statistical Analysis

Differences in demographic factors and neuropsychological test scores were analyzed using non-parametric tests; the Kruskal–Wallis test for continuous data, and Fisher's Exact test for categorical data.

Imaging Protocol

All examinations were performed with a 3.0T MR system (Magneton Verio, Siemens Medical Systems, Erlangen, Germany) with an orthonormal head coil. During the MRI scan, all participants were asked to remain still in the supine position with the surrounding space being filled with sponge.

We here relied on diffusion weighted images (DWI) and rsfMRI data with the following parameters: DWI: b1 = 0 s/mm^2, b2 = 1,000 s/mm^2, b3 = 2,000 s/mm^2/64 directions, Matrix = 112 × 112, FOV = 224 mm × 224 mm, TR = 2,400 ms, TE = 71 ms, 76 slices, 2 mm thickness, no gap. and rsfMRI: TR = 500 ms, TE = 30 ms, flip angle (FA) = 60°, FOV = 224 mm × 224 mm, matrix = 64 × 64, slices = 35, thickness = 3.5 mm, gap = 0.5 mm. A 3D MPRAGE (magnetization prepared rapid acquisition gradient echo) image (voxel size 1 mm × 1 mm × 1 mm, TE: 2.98 ms, TR: 2,530 ms, flip angle = 7°) was also obtained.

Diffusion Tractography Preprocessing Steps

The DWI images were processed using the Infinitome software (Omniscient Neurotechnology, 2020), which employs standard processing steps in the Python language. The processing pipeline includes the following: (1) the diffusion image is resliced to ensure isotropic voxels, (2) motion correction is performed using a rigid body registration algorithm to a baseline scan, (2) slices with excess movement (defined as DVARS > 2 sigma from the mean slice) are eliminated, (3) the T1 image is skull stripped using the HD-BET software (Isensee et al., 2019), which is inverted and aligned to the DWI image using a rigid alignment, which is then used as a mask to skull strip the aligned DWI image, (4) gradient distortion correction is performed by applying a diffeomorphic warping registration method between the DWI and T1 images, (5) The fiber response function is estimated and the diffusion tensors are calculated using constrained spherical deconvolution, (7) deterministic tractography is performed with uniform random seeding, 4 seeds per voxel, usually creating about 300,000 streamlines per brain.

Creation of a Personalized Brain Atlas Using Machine Learning Based Parcelation

In order to minimize the effects of gyral variation, we used a machine-learning based, subject specific version of the Human Connectome Project Multimodal Parcelation (HCP-MMP1) atlas (Glasser et al., 2016) generated based on each subject's structural connectivity, which has been described elsewhere (Doyen et al., 2022). **Figure 1** demonstrates the steps in creation of this personalized atlas. Briefly, a machine learning model was trained by entering preprocessed tractography data from 178 healthy controls obtained from the SchizConnect database to learn the structural connectivity pattern between voxels included within the 379 parcels of the HCP-MMP1 atlas. The same unaltered atlas was then warped onto each brain of the study sample. The trained machine learning model was then applied to each individual in the study sample to appoint voxels located at the endpoint of tractography streamlines to their most likely warped HCP parcelation based on the structural connectivity feature vectors, resulting in reparcelation of voxels. This method creates a version of the HCP-MMP1 atlas with 180 cortical parcels and 9 subcortical structures per hemisphere, along with the brainstem as one parcel.

We mapped the identified parcels to known resting-state networks based on the hierarchical structure described by Akiki and Abdallah (2019): the Default Mode Network (DMN), the

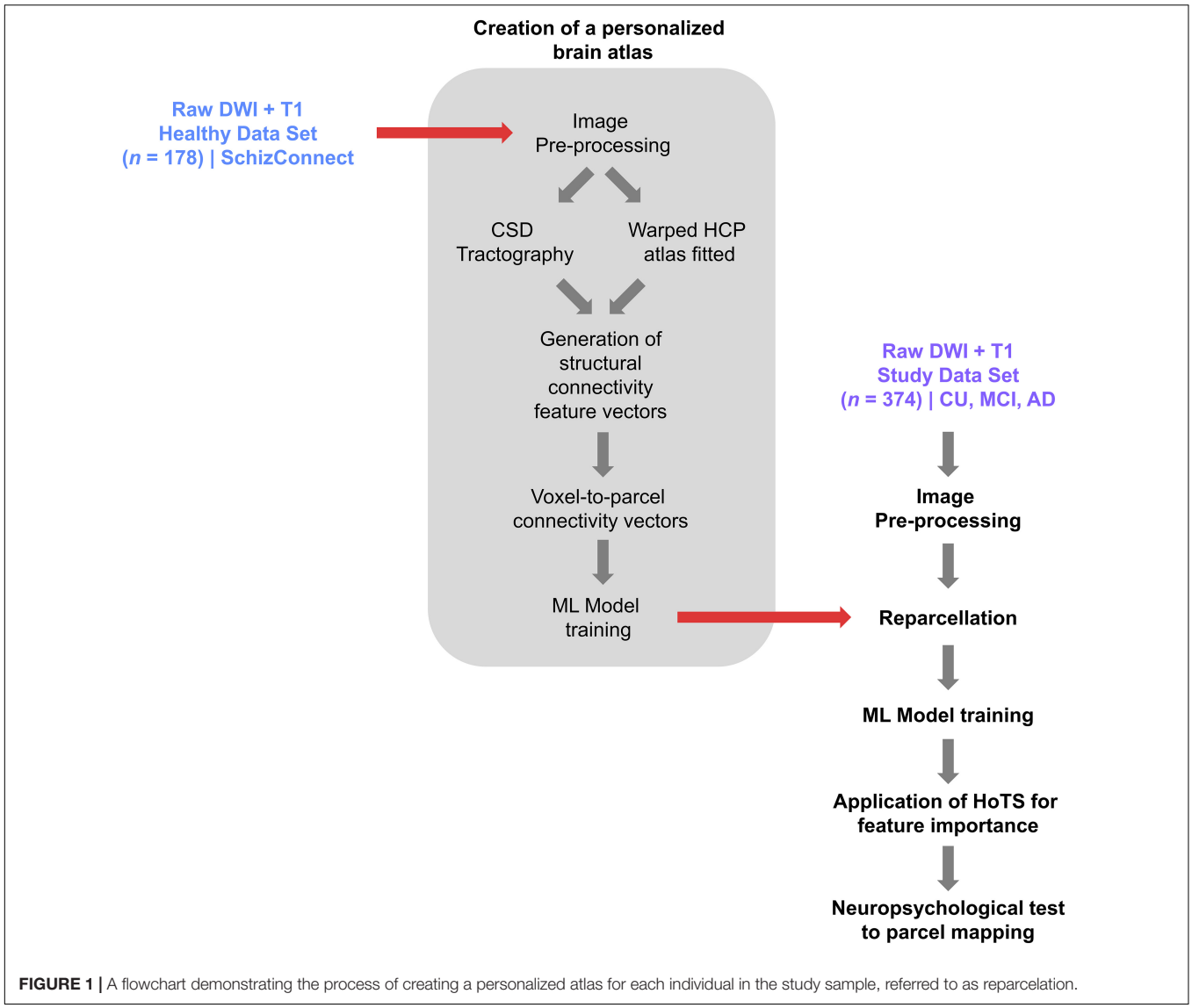

FIGURE 1 | A flowchart demonstrating the process of creating a personalized atlas for each individual in the study sample, referred to as reparcelation.

Central Executive Network (CEN), Dorsal Attention Network (DAN), Salience Network (SN), Sensorimotor Network (SMN), and Visual Network (VN). These networks are based on the model first demonstrated by Yeo et al. (2011), who mapped specific parts of the cortex to known large-scale networks (Yeo et al., 2011). These networks have since been investigated across the spectrum of healthy and pathological cognitive states and have been demonstrated to underlie key cognitive processes. This template was therefore applied to our dataset to investigate patterns in the identified brain regions, and the networks with which they are associated.

rsfMRI Preprocessing Steps

The rsfMRI images were processed using standard processing steps including: (1) motion correction on the T1 and BOLD images using a rigid body alignment, (2) elimination of slices with excess movement (defined as DVARS > 2 sigma from the mean slice), (3) skull stripping of the T1 image using a convolutional neural net (CNN), which is inverted and aligned to the resting state bold image using a rigid alignment, and used as a mask to skull strip the rsfMRI image, (4) slice timing correction, (5) Global intensity normalization, (6) gradient distortion correction using a diffeomorphic warping method to register the rsfMRI and T1 images, (7) High variance confounds are calculated using the CompCor method (Behzadi et al., 2007); these confounds as well as motion confounds are regressed out of the rsfMRI image, and the linear and quadratic signals are detrended. Note this method does not perform global signal regression, (8) spatial smoothing is performed using a 4 mm FWHM Gaussian kernel. The personalized atlas created in previous steps is registered to the T1 image, and gray matter atlas regions are aligned with the gray matter regions in each subject's scans. Thus, it is ideally positioned for extracting a BOLD time series, averaged over all voxels within a region, from all 379 regions (180 parcels from two hemispheres, plus 19 subcortical structures). The Pearson correlation coefficient is calculated between the BOLD signals

of each unique area pair (self to self-inclusive), which yields 143,641 correlations.

Mapping of Neuropsychiatric Tests to Brain Regions Using the Hollow-Tree Super Method

We subsequently built machine learning models to predict a subject's performance on a given test based on their functional connectome. The black box problem in machine learning generally limits the ability to utilize machine learning techniques in clinical practice, as there is generally a need-to-know which parts of the brain contribute to a given pathology. In order to address this, we used a boosted trees approach, called Hollow-tree Super (HoTS) (Doyen et al., 2021), to determine which features of each machine learning model, in this case the functional connectivity among brain regions, were contributing most to the model's prediction of performance on each neuropsychological test. Performance in each test was classified by a tertile split, with the upper and lower tertiles classed as poor and good performance, respectively. The binarization of these test scores was necessary to apply logistic regression to continuous scores. However, since the mapping of psychometric testing to brain regions using machine learning is a novel technique, the thresholds were chosen to reflect differences between the worst and best performing groups. This was done to ensure that the model was identifying biological differences which were reflective of the clear functional differences between these two groups. Test specific tertile limits were: MOCA-B ($<$ 17, poor performance; $>$ 24 good performance), the Clock Drawing Test ($<$ 3, poor performance; 3, good performance), and the Hopkins Verbal Learning Test Delayed Recall (0, poor performance; $>$ 6, good performance). The prediction performance of each model was measured by the area under the receiver-operator curve (AUC-ROC). The binarization of each test and the class balances are provided in the **Supplementary Figures**.

RESULTS

Patient Characteristics

Table 1 shows the demographic characteristics and median neuropsychological test scores, along with significance of differences reported on Kruskal–Wallis and Fisher's Exact Tests. Across groups, there were significant differences in age and education between control, MCI and AD subjects, with control subjects being generally younger (median $\pm$ IQR, 71 $\pm$ 10 in control; 72 $\pm$ 11 in MCI; and 75 $\pm$ 10 in AD) and having attained a greater number of years of education (12 $\pm$ 6 in control; 9 $\pm$ 3 in MCI; 9 $\pm$ 3 in AD). Additionally, there were significant group differences in all neuropsychological tests conducted, with MCI and AD subjects performing worse.

Machine Learning Reveals Parcels Underlying Cognitive Deficits

Applying our HoTS methodology to determine features of the functional connectome associated with performance in each neuropsychological test, eleven models had a test AUC greater than 0.65 (**Figure 2A**): Boston Naming Test (BNT), Boston Naming Test—Articulateness and Fluency (BNT-A), Hopkins Verbal Learning Test Immediate Recall (HVLT-I), Hopkins Verbal Learning Test 5 min Delayed Recall (HVLT-D), Rey Osterrieth Complex Figure Imitation (ROCF-I), Rey Osterrieth Complex Figure Recall (ROCF-R), Shape Trail Test Part A (STT-A), Shape Trail Test Part B (STT-B), Wechsler Memory Scale Logical Memory (WMS-LM), Clock Drawing Test (CDT), and

TABLE 1 | Subject demographics.

	Control (n = 140) Median (IQR)	MCI (n = 149) Median (IQR)	AD (n = 85) Median (IQR)	p-value
Age (years)	71 (65, 75)	72 (70, 81)	75 (67, 77)	<0.001
Education (years)	12 (9, 15)	9 (9, 12)	9 (9, 12)	<0.001
Sex n (%)				0.130
Female	68 (48.6)	81 (54.7)	53 (62.4)	
Male	72 (51.4)	67 (45.3)	32 (37.6)	
Missing	0	1	0	
MMSE	27.5 (26, 28)	24 (22, 26)	15 (11, 19)	<0.001
MOCA-B	24 (22, 26)	16 (14, 19)	8 (5, 11)	<0.001
Wechsler Memory Scale Logical Memory	9 (7, 11)	6 (4, 7.25)	2 (1, 4)	<0.001
Hopkins Verbal Learning Test (Immediate)	19 (16, 22)	14 (11, 17)	7 (3, 10)	<0.001
Hopkins Verbal Learning Test (Delayed 5 min)	7 (5, 8)	3 (0, 5)	0 (0, 0)	<0.001
Hopkins Verbal Learning Test (Delayed 20 min)	7 (5, 8)	3 (0, 5)	0 (0, 0)	<0.001
Boston Naming Test	24 (20, 26)	21 (17, 24)	15 (11.5, 20)	<0.001
Boston Naming Test Articulateness and Fluency	15 (12, 17)	12 (9, 14)	6 (4, 9)	<0.001
Rey Osterrieth Complex Figure Imitation	32 (6, 35)	21 (6, 33.5)	6 (1, 22)	<0.001
Rey Osterrieth Complex Figure Recall	11 (5, 19)	4 (0, 10)	0 (0, 0)	<0.001
Shape Trail Test Part A	56 (44, 73)	73 (58, 94.75)	108.5 (80.75, 140.5)	<0.001
Shape Trail Test Part B	145 (109, 179)	181 (153, 230)	232 (189.5, 273)	<0.001

Non-parametric tests conducted, with median and interquartile range (IQR) reported. MCI, mild cognitive impairment; AD, Alzheimer's Disease.

MOCA-B. Results were categorized into the domains of Language (BNT), Verbal Learning and Memory (HVLT-I, HVLT-D, WMS-LM), Attention and Executive Function (BNT-A, STT-A, STT-B), Visuospatial Function (ROCF-I, ROCF-R, CDT), and MOCA-B as a standalone general cognitive test.

Injury to Sensory and Higher Order Association Regions Underlie Naming Deficits in AD

Right 3a (SMN), right 10r (DMN), left OP1 (SMN), and left 9–46 days (SN) were most predictive of poor performance in the BNT, whereas there were no predictors of absence of deficit. **Supplementary Figure 1** shows the log odds of each parcel as a predictor for performance in the BNT.

DLPFC and IFOF-Connected Regions Are Abnormal in People With Impaired Verbal Recall

Table 2 lists the parcels identified by each model for tests associated with verbal learning and memory. Poor performance in the HVLT-I was associated with multiple core networks, including DMN, CEN, SN, and VN. Anatomically, a subset of these parcels were in the right dorsolateral prefrontal cortex (DLPFC) (right 8Av, right 8Ad, right p9-46v), right premotor area (area 6d, area 6a, area 6r), right insula (right PoI2), left DLFPC (left 46), left medial frontal lobe (left 10r) and left occipital cortex (left V1, left V3B, left FST). The distribution of these parcels suggest that the model may be highlighting alterations in the connectivity of the inferior fronto-occipital fascicle (IFOF). Expectedly, absence of deficit in the HVLT-I was linked to regions associated with working memory: left PHA1, left p10p, and left 23 days.

Deficits in Delayed and Episodic Verbal Recall Highlight Possible Functional Compensation

The CEN and DMN were most associated with deficits in the HVLT-D, whereas the VN, SN, and DMN were linked to absence of deficits. Notably, the right-sided analogs of speech areas, right 55b, and right 45 were associated with absence and presence of deficit, respectively.

When looking at the substrates for verbal episodic memory, presence of deficit in the WMS-LM was associated with the DMN, CEN, SMN and VN; while absence of deficit was associated with parcels in the medial temporal lobe and limbic components of the DMN, CEN, SN and the right Amygdala. **Supplementary Figures 2–4** show the log odds of each parcel as a predictor for performance in each language test.

Performance in Executive Function Is Associated With Executive and Sensory Networks

The parcels our models associated with performance in tests associated with attention and executive function are listed in **Table 3**. For the BNT-A, parcels predictive of deficit were affiliated with the CEN, DMN, DAN, and SMN. Conversely, parcels associated with absence of deficit were mostly associated with the DMN, especially its limbic components.

Furthermore, deficits in the STT-A were associated with several networks, including the DMN, CEN, DAN, and SMN, while absence of deficit was predicted by parcels in the CEN, and SMN. In the STT-B, the DAN, CEN, DMN, SMN, and VN were associated with deficit; whereas the SN, DAN and SMN were associated with absence of deficit. Both tests demonstrate impairment in areas known to be associated with executive function, though there was also involvement of unexpected networks such as the SMN. **Supplementary Figures 5–7** detail the feature importance of each parcel as a predictor in the models for the attention and executive function tests.

Visuospatial Deficits Are Associated With Multiple Large-Scale Networks

Table 4 shows the identified parcels associated with performance in visuospatial tests, along with their network affiliation. Presence of deficit in the ROCF-I was mainly associated with subcortical structures and SN; while absence of deficit was mostly linked to the VN and DMN. Functional connectivity of parcels in the DAN and VN were predictors of deficit in ROCF-R, whereas absence of deficit was linked to the limbic and language components of the DMN and CEN.

Moreover, language regions of the DMN and the SMN were associated with deficit in the CDT, whereas the SMN, CEN, and DMN were associated with absence of deficit.

Log odds of each parcel as a predictor of performance for the visuospatial tests are shown in **Supplementary Figures 8–10**.

Parcels Associated With Performance in MOCA-B May Provide Markers of Cognitive Decline

Finally, poor performance in the MOCA-B was associated with the CEN (right 13l, left POS2, right 8Av, right p9-46v, left PFm), VN (left V1, right VIP, left V7), and SMN (right 4, right Pir, left 7PC); and absence of deficit was linked to the SMN (right FOP2, left MBelt), SN (left FOP1), DMN (right PCV) and VN (right PIT). Although the AUC of 0.68 for this model was relatively low, these areas may be studied further as possible markers to predict cognitive decline. The log odds for each parcel is provided in **Supplementary Figure 11**.

Overlaps and Differences Across Cognitive Domains May Provide Insight Into Distinct Progression Trajectories in AD

We next explored overlaps between parcels associated with each neuropsychological test to derive patterns which may aid in diagnosis. At a network level, predictors of deficit in each test were affiliated with a variety of networks, although the CEN was most common, followed by the DMN (**Figure 2B**). We identified 20 parcels which were predictors of poor performance in at least two neuropsychological tests (**Figure 2C**). Most of these were affiliated with the CEN, DMN, and DAN. When examining parcels associated with

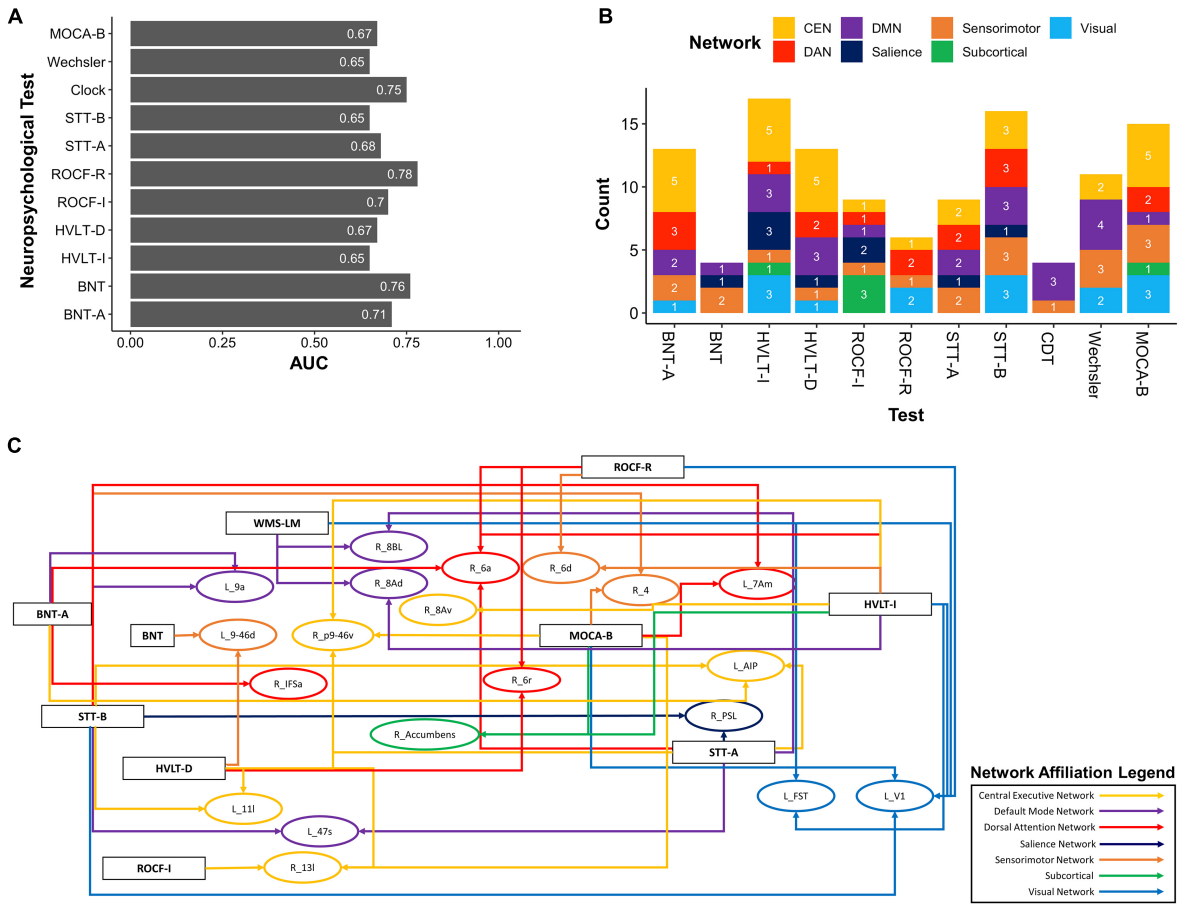

FIGURE 2 | Baseline resting-state fMRI parcels predicting deficits in neuropsychological tests. **(A)** 11 neuropsychological tests surpassed an AUC of 0.65. **(B)** Parcel to network mapping showed that parcels in the CEN and DMN were most frequently associated with poor performance in neuropsychological testing, though other networks were also represented. **(C)** Neuropsychological test to parcel mapping of twenty parcels which were predictors of at least two tests. The parcels have been placed in relative anatomical positions, while the colors of the arrows represent the networks associated with the parcels. Each arrow is drawn from the neuropsychological test (rectangle) to a single parcel (oval). CEN, Central Executive Network; DAN, Dorsal Attention Network; DMN, Default Mode Network; BNT-A, Boston Naming Test—Articulateness and Fluency; BNT, Boston Naming Test; HVLT-I, Hopkins Verbal Learning Test—Immediate Memory; HVLT-D, Hopkins Verbal Learning Test—Delayed Recall; ROCF-I, Rey Osterrieth Complex Figure Imitation; ROCF-R, Rey Osterrieth Complex Figure Recall; STT-A, Shape Trail Test—Part A; STT-B, Shape Trail Test Part B.

absence of deficit, the DMN and CEN were also over-represented (**Figure 3A**). 14 parcels were predictors of good performance in at least two neuropsychological tests (**Figure 3B**), and most parcels were associated with temporal structures affiliated with the DMN.

Although each neuropsychological test assesses distinct functions, to identify commonalities and differences in our data, we grouped parcels by the cognitive domain associated with each test. We then identified parcels which were predictors of performance in at least two neurocognitive tests within each domain. Language and the MOCA-B were left out of this analysis as only one model was associated with each of these. Within Verbal Learning and Memory, four out of six parcels were associated with poor performance in at least two tests, whereas right 6d was associated with poor performance in the WMS-LM and good performance in HVLT-I, and left 23d was associated with good performance in both the WMS-LM and HVLT-I (**Figures 4A,B**). Common parcels associated with attention and executive function were located within the frontal and parietal lobes (**Figures 4C,D**). All parcels were associated with poor performance, except right 43, which was associated with poor performance in the STT-A, but good performance in STT-B. Given the difference between the two tasks is the cognitive flexibility required in STT-B, which is the harder task, this region may be indicating initial functional compensation which is successful in some individuals. Finally, all common parcels associated with visuospatial function were in the temporooccipital region, with the addition of the right Thalamus (**Figures 4E,F**). All parcels identified were common predictors of absence of deficit, except right V8, which was associated with absence of deficit in the CDT and presence of deficit in the ROCF-D; and left EC, which was associated with absence of deficit in the CDT and presence of deficit in the ROCF-I. These differences may again be indicative of different stages or

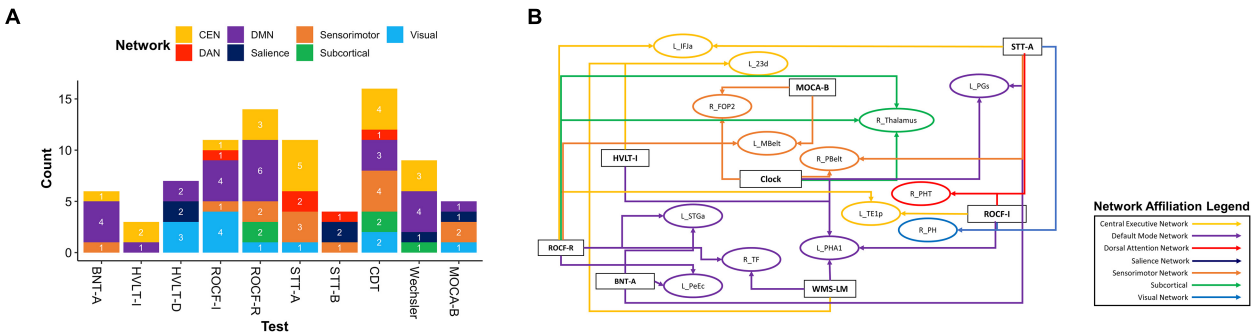

FIGURE 3 | Baseline resting-state fMRI parcels predicting absence of deficits in neuropsychological tests. **(A)** Parcel to network mapping showed that parcels in the CEN and DMN were most frequently associated with absence of deficit in neuropsychological testing, and these networks were the most common overall. **(B)** Neuropsychological test to parcel mapping of fourteen parcels which were predictors of good performance in at least two tests. The parcels have been placed in relative anatomical positions, while the colors of the arrows represent the networks associated with the parcels. Each arrow is drawn from the neuropsychological test (rectangle) to a single parcel (oval). CEN, Central Executive Network; DAN, Dorsal Attention Network; DMN, Default Mode Network; BNT-A, Boston Naming Test—Articulateness and Fluency; BNT, Boston Naming Test; HVLT-I, Hopkins Verbal Learning Test—Immediate Memory; HVLT-D, Hopkins Verbal Learning Test—Delayed Recall; ROCF-I, Rey Osterrieth Complex Figure Imitation; ROCF-R, Rey Osterrieth Complex Figure Recall; STT-A, Shape Trail Test—Part A; STT-B, Shape Trail Test Part B.

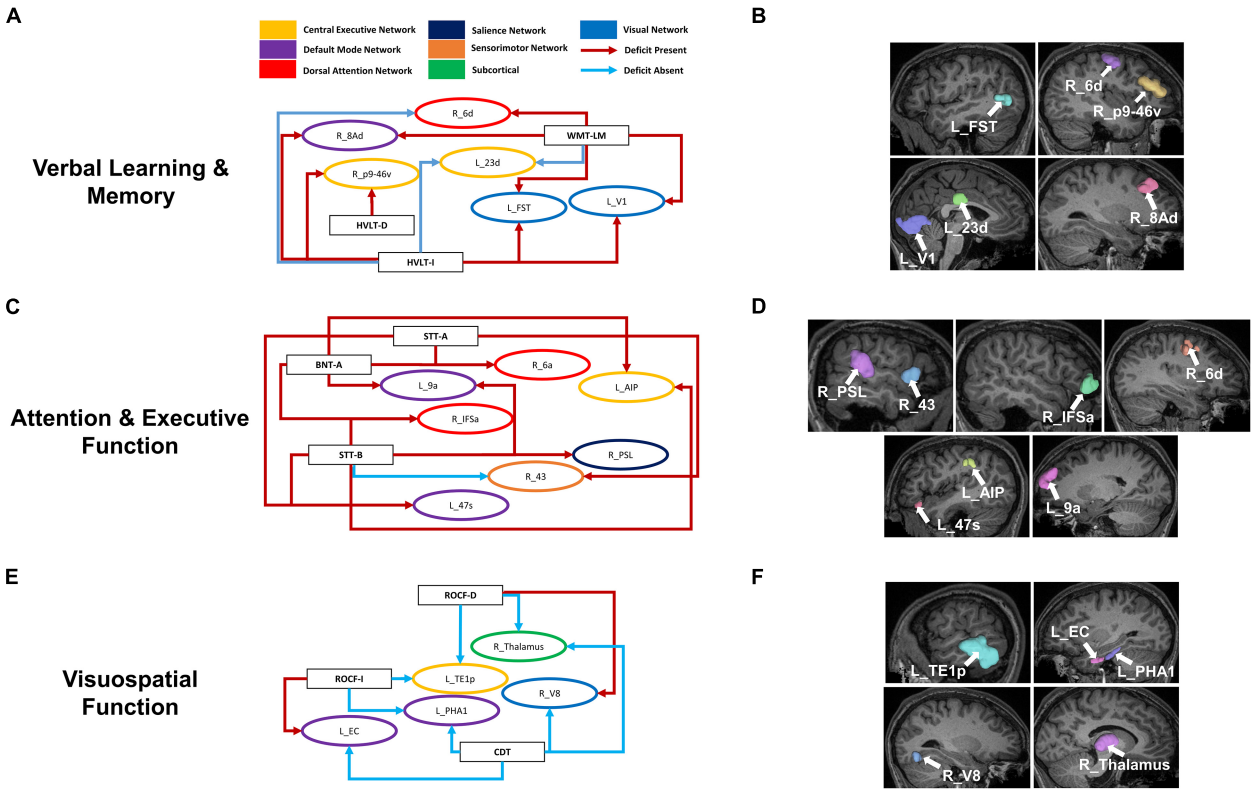

FIGURE 4 | Overlaps within cognitive domains may provide insight into functional compensation and cognitive trajectories in AD. Parcels associated with performance in at least two neurocognitive tests associated within each cognitive domain: Verbal Learning and Memory **(A)**, Attention and Executive Function **(C)**, and Visuospatial Function **(E)**. Each arrow is drawn from the neuropsychological test (rectangle) to a single parcel (oval). The arrows are colored by whether the association was to poor performance (Deficit Present) or good performance (Deficit Absent) as defined in the methodology for each test, while the parcels are colored by their associated networks. Anatomical locations of the given parcels are also shown on a T1 MRI **(B,D,F)**. BNT-A, Boston Naming Test—Articulateness and Fluency; BNT, Boston Naming Test; HVLT-I, Hopkins Verbal Learning Test—Immediate Memory; HVLT-D, Hopkins Verbal Learning Test—Delayed Recall; ROCF-I, Rey Osterrieth Complex Figure Imitation; ROCF-R, Rey Osterrieth Complex Figure Recall; STT-A, Shape Trail Test—Part A; STT-B, Shape Trail Test Part B, WMS-LM, Wechsler Memory Scale—Logical Memory.

TABLE 2 | Predictors of performance in neuropsychiatric tests associated with verbal learning and memory.

Wechsler Memory Scale				Hopkins Verbal Learning Test Immediate Memory				Hopkins Verbal Learning Test Delayed Recall			
AUC = 0.65				AUC = 0.65				AUC = 0.67			
Deficit Present		Deficit Absent		Deficit Present		Deficit Absent		Deficit Present		Deficit Absent	
Area	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**
L_V1	Visual	L_PHA1	DMN	R_H	DMN	L_PHA1	DMN	L_9-46d	Salience	L_PIT	Visual
R_TE1p	CEN	R_TF	DMN	R_23d	CEN	L_p10p	CEN	R_LIPd	CEN	L_23c	Salience
R_6d	SMN	R_AAIC	CEN	R_8Av	CEN	L_23d	CEN	R_6r	DAN	L_9m	DMN
R_47m	DMN	R_9a	DMN	R_6a	DAN			L_11l	CEN	R_TPOJ1	DMN
L_FST	Visual	L_MI	Salience	R_pOFC	CEN			R_7AL	SM	R_55b	Salience
R_8BL	DMN	L_RSC	CEN	R_6d	SM			R_45	DMN	R_LO2	Visual
R_11l	CEN	R_PHA1	DMN	R_Accumbens	SC			L_10pp	DMN	L_VMV2	Visual
L_1	SMN	L_23d	CEN	L_FST	Visual			L_PEF	DAN		
L_3b	SMN	R_Amygdala	SC	L_V1	Visual			R_PGs	CEN		
R_STSva	DMN			R_8Ad	DMN			R_13l	CEN		
R_8Ad	DMN			L_IFJp	CEN			R_V4t	Visual		
				L_SCEF	Salience			R_p9-46v	CEN		
				L_V3B	Visual			L_p32	DMN		
				R_PoI1	Salience						
				L_10r	DMN						
				R_p9-46v	CEN						
				L_46	Salience						

CEN, Central Executive Network; DAN, Dorsal Attention Network; DMN, Default Mode Network; SC, Subcortical Deficit Present refers to good performance, whereas Deficit Absent refers to poor performance in a given test, as defined in the methodology.

trajectories of disease, though the lack of longitudinal data limited further analysis.

We finally looked at commonalities between domains by classifying the 20 parcels associated with presence of deficit in two or more tests into five domains based on the associated neuropsychological test (**Figure 5A**). The common areas tended to be in the frontal lobe and affiliated with the CEN (right p9-46v, right 13l, right 8Av, left 11l), DAN (right 6a, right 6d) DMN (right 8BL, left 7Am), SMN (right 4, right 6a), SN (left 9–46d), and right Accumbens. Interestingly, we noted a convergence of verbal learning and visuospatial function at areas right 6a, right 6d and right 6r. Furthermore, a similar grouping of parcels associated with absence of deficit (**Figure 5B**) revealed several temporal and perisylvian regions within the DMN (R_TF, R_PHA1, left PGs, left STGa), SMN (left MBelt, right PBelt, right FOP2), DAN (right PHT), CEN (left IFJa) and VN (right PH).

DISCUSSION

Despite rising prevalence and ongoing efforts, we still lack adequate tools to track the progression of MCI and diagnose AD early in its pathological stage. Data-driven methods are needed to *a priori* identify pathological progression and functional decline and enable premorbid treatment. Our machine learning models demonstrate that different neurocognitive deficits in AD are associated with functional connectivity abnormalities in multiple bi-hemispheric neural networks. Notably, the limbic components of the DMN and CEN, and the DAN were most associated with performance measures. Deficits in multiple domains revealed impairments in top-down processing, and possible recruitment of analog areas in the contralateral hemisphere, which may underlie response to injury in AD. We propose these regions may serve as possible neuroimaging markers of disease progression, and aid in establishing clinical trajectories, though longitudinal data are needed to explore this further. Ultimately, we demonstrate the utility of data-driven methods to explore the neural networks underlying functional and cognitive deficits in AD. Further analyses have the potential to revolutionize diagnosis and treatment, and improve quality of life in AD.

Cognitive Deficits in AD Arise From Impairment in Multiple Networks

A commonality between all the models in our analysis was the involvement of multiple networks in each cognitive task, and the involvement of areas which would not classically be associated with a given task. For example, deficits in naming were associated with regions outside of language or motor planning areas. Similarly, our data suggest that fluency and articulation deficits in AD may be caused by cognitive abnormalities in motor planning, with several premotor area parcels being associated with deficit. The same premotor regions were also associated with visuospatial deficits in our dataset. Previous studies have identified a possible role of the premotor area in articulation planning (Paulesu et al., 1993; Marvel and Desmond, 2012; Liao et al., 2014). This may suggest that fluency and articulation difficulties in AD stem from a phenomenon paralleling ideational apraxia,

TABLE 3 | Predictors of performance in neuropsychiatric tests associated with attention and executive function.

Boston naming test articulateness and fluency				Shape trail test (Part A)				Shape trail test (Part B)			
AUC = 0.71				AUC = 0.68				AUC = 0.65			
Deficit Present		Deficit Absent		Deficit Present		Deficit Absent		Deficit Present		Deficit Absent	
Area	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**
R_IFSa	DAN	R_IFJp	CEN	L_47s	DMN	L_IFJa	CEN	L_47s	DMN	R_FOP1	Salience
R_47s	DMN	L_PGs	DMN	L_13l	CEN	R_PH	Visual	L_11l	CEN	L_p32pr	Salience
L_9a	DMN	L_STGa	DMN	R_LBelt	SMN	R_PFt	DAN	L_V3CD	Visual	R_TE2p	DAN
R_2	SMN	R_OP2-3	SMN	L_AIP	DAN	L_p47r	CEN	R_a9-46v	CEN	R_43	SMN
L_6mp	SMN	L_PeEc	DMN	R_p9-46v	CEN	R_PHT	DAN	L_AIP	DAN		
L_LIPv	Visual	R_H	DMN	R_PSL	Salience	L_PFm	CEN	L_7Am	DAN		
R_6a	DAN			R_6a	DAN	R_PBelt	SMN	L_s6-8	CEN		
R_OFC	CEN			R_8BL	DMN	L_p24	CEN	R_STSdp	DMN		
L_IFSa	CEN			R_43	SMN	L_Pir	SMN	R_PSL	Salience		
L_d32	DMN					R_8BM	CEN	L_V1	Visual		
R_9-46d	CEN					R_RI	SMN	L_PFcm	SM		
L_AVI	CEN							L_PH	Visual		
L_AIP	DAN							L_9a	DMN		
								R_4	SMN		
								R_TA2	SMN		
								R_IFSa	DAN		

CEN, Central Executive Network; DAN, Dorsal Attention Network; DMN, Default Mode Network; SC, Subcortical Deficit Present refers to good performance, whereas Deficit Absent refers to poor performance in a given test, as defined in the methodology.

TABLE 4 | Predictors of performance in neuropsychiatric tests associated with visuospatial function.

Rey osterrieth complex figure imitation				Rey osterrieth complex figure recall				Clock drawing test			
AUC = 0.70				AUC = 0.78				AUC = 0.75			
Deficit present		Deficit Absent		Deficit Present		Deficit absent		Deficit Present		Deficit absent	
Area	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**	**Area**	**Network**
R_Caudate	SC	L_TE1p	CEN	L_OFC	CEN	L_TGd	DMN	L_31a	DMN	L_PBelt	SMN
L_p32pr	Salience	L_SFL	DMN	R_6r	DAN	R_V1	Visual	L_STSva	DMN	R_TE1m	CEN
Brainstem	SC	R_Pol2	SMN	R_6a	DAN	L_TE1p	CEN	L_44	DMN	L_Thalamus	SC
L_Caudate	SC	L_PHA1	DMN	R_V8	Visual	L_STGa	DMN	R_5m	SMN	L_PGs	DMN
L_EC	DMN	R_PHT	DAN	R_6d	SMN	R_STSda	DMN			R_V8	Visual
R_13l	CEN	R_PH	Visual	L_V1	Visual	L_Accumbens	SC			R_IP2	CEN
L_PF	Salience	L_PHA3	DMN			L_TE1a	DMN			L_PHA1	DMN
L_5L	SMN	R_V2	Visual			L_a32pr	CEN			L_EC	DMN
R_PFt	DAN	L_VIP	Visual			R_TF	DMN			L_5m	SMN
		L_LIPv	Visual			R_OP1	SMN			R_9-46d	CEN
		L_8Av	DMN			L_MBelt	SMN			L_TE2p	DAN
						R_Thalamus	SC			L_IP1	CEN
						L_IFJa	CEN			R_PBelt	SMN
						L_PeEc	DMN			L_VVC	Visual
										R_FOP2	SMN
										R_Thalamus	SC

CEN, Central Executive Network; DAN, Dorsal Attention Network; DMN, Default Mode Network; SC, Subcortical Deficit Present refers to good performance, whereas Deficit Absent refers to poor performance in a given test, as defined in the methodology.

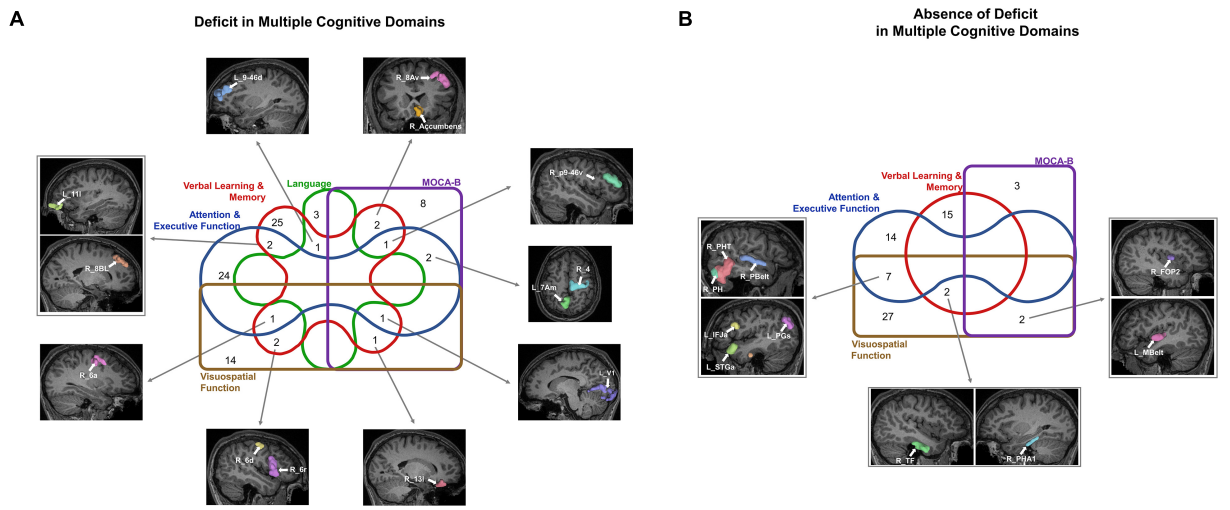

FIGURE 5 | Commonalities across cognitive domains may provide potential targets for screening, diagnosis, and treatment. The Venn diagrams show the parcels which are predictors of **(A)** deficit and **(B)** absence of deficit across at least two cognitive domains.

rather than exclusively explicit damage to language areas. Overall, these data suggest that many deficits in AD present a multi-network cognitive problem, rather than localized functional deficits. A multi-network perspective of functional deficits in AD must be assumed when describing the disease which should underlie the development of any therapeutic intervention.

The Role of the DLPFC and IFOF in Working Memory

Several parcels within the DLPFC were associated with poor performance in the immediate recall portion of the HVLT. The DLPFC bilaterally is known to play an important role in verbal and spatial working memory (Sisi and Yixuan, 2018). In AD, impaired plasticity of the left DLPFC, measured as potentiation of cortical evoked activity has been correlated with working memory (Kumar et al., 2017). Increased activation of the right DLPFC on the other hand has also been associated with memory deficits in AD (Erk et al., 2011; Liang et al., 2011). Whether this is a maladaptive or compensatory mechanism remains unclear. Our model for poor performance in the HVLT-I predominantly highlighted the right DLPFC, which may indicate a similar maladaptive reorganization or nociferous compensation.

Furthermore, our machine learning model associated the functional connectivity of parcels in the left occipital and frontal lobes with impaired immediate recall. The IFOF is a white matter bundle which runs between these two regions, connecting the frontopolar, orbitofrontal and inferior frontal cortices to the occipital lobe (Conner et al., 2018). The role of the IFOF remains controversial. Several neuroimaging and neuromodulation studies have suggested a role in visual semantic processing (Moritz-Gasser et al., 2013; Almairac et al., 2015; Yordanova et al., 2017). However, it is still unclear how this pathway functionally differs from the parallel, indirect path in the ventral stream, anatomically described as the inferior longitudinal fascicle (ILF)/uncinate fasciculus (UF). Since the IFOF is connected to executive areas in the frontal lobe, it is possible that the IFOF is primarily involved in top-down processing of language, whereby the frontal lobe aids in visual semantic processing by biasing the visual system toward cognitively relevant goals. Indeed, planning spoken language has been shown to require attentional control (Roelofs and Piai, 2011). Our data may therefore be pointing to a similar paradigm, whereby individuals performing poorly on a verbal working memory task have left IFOF deficits. The model for deficits in HVLT-I also identified the right insula. This may be suggestive of ineffective compensation by the right IFOF, which also has subinsular components, however, further functional and lesion studies are required to investigate these hypotheses.

Modulating Compensatory Plasticity in AD

Our models highlighted several possible compensatory mechanisms underlying deficits in MCI and AD, including the recruitment of alternate networks and contralateral analogous areas. Further exploring these changes in functional connectivity hold potential in targeting neuroplastic responses to injury in AD. Congruent to this, a recent study on a small cohort of patients with subjective cognitive decline (SCD), MCI, and AD demonstrated decrease in functional connectivity centrality measures in the somatomotor and visual networks in SCD patients (Wang et al., 2019). In contrast, AD patients showed an increase in centrality measures, and the authors proposed that as associative networks such as the DMN, CEN, and DAN were damaged, there was attempted compensation in the primary sensory networks. The frequent association of the sensorimotor and visual networks with presence of deficit within our data may therefore be explained by maladaptive recruitment of these networks in AD patients. These findings were echoed by another study demonstrating increased connectivity within the prefrontal, parietal and occipital lobes in AD, alongside

decreased connectivity between the frontal and prefrontal lobes (Wang et al., 2007). This phenomenon of anterior-posterior functional connectivity dysfunction (Tao et al., 2020) may also be reflected in our data set, as many parcels which were predictors of dysfunction in multiple tests were in the parietal and frontal cortices. Moreover, the use of functional connectivity measures in the diagnosis and treatment of AD may enable precision medicine to improve patient outcomes. Functional connectivity may be a marker of cognitive reserve (Topiwala et al., 2019; Ewers et al., 2021), a hypothesis which may underpin the different clinical trajectories seen in AD (van Loenhoud et al., 2019). Indeed, patients with higher cognitive reserve were seen to have a more efficient functional connectome, suggesting they are better able to cope with progressing AD pathology (Weiler et al., 2018). Exploring the individual differences in the ability of the brain to adapt to network changes may enable harnessing methods to improve compensation in response to AD.

Predicting MCI Conversion to AD

There have been several studies demonstrating the utility of machine learning tools in predicting MCI conversion to AD, and in diagnosing AD, with varying degrees of success (Syaifullah et al., 2020; Kumar et al., 2021). Each study utilizes a different combination of features in their models, ranging from clinical data, neuropsychological testing (Battista et al., 2017; Gupta and Kahali, 2020), behavioral and psychiatric data (Gill et al., 2020; Lo et al., 2020), and various imaging modalities (Jo et al., 2019). It is however unclear how early these models can be employed to screen individuals. The heterogeneity in clinical trajectories, and the likely need to implement treatment much earlier than the onset of symptoms require biological markers which indicate risk prior to decline in neuropsychological testing. This accounts for the popularity of incorporating imaging modalities into many of these models, as they provide a minimally invasive means of diagnosis independent of neuropsychological testing. The strength of the present study is the ability of our machine learning model to provide visibility into the features of the functional connectome associated with cognitive function. In fact, the neuroanatomical information provided by this method, specifically the areas of coherent overlap between domains as highlighted in **Figure 5**, and differences within, and across domains can be integrated with the neuropathological perspective in AD to build a progression model which can be used in screening and diagnosis. For example, Vogel et al. (2021) identified four trajectories in AD based on tau deposition. Rate of tau deposition has also been associated with functional connectivity in AD (Franzmeier et al., 2020) and functionally connected regions demonstrated shared levels of tau (Franzmeier et al., 2019), The close link between tau deposition and cognitive decline warrants further exploration of the role of functional connectivity in tau progression in AD. While some regions we identified overlapped with common areas of β-amyloid and tau deposition (Braak and Braak, 1991; Braak et al., 2011), it is not possible to apply pathological models without longitudinal data, and on a mixed cohort of AD and MCI patients. Nonetheless, our methods can enable an exploration of the differential effects of β-amyloid and tau deposition and provide means of predicting pathological progression *in vivo*.

Machine Learning Models in AD

It is difficult to directly compare the performance of our model to models used in previous studies. While most studies utilize machine learning to classify patients into a diagnostic category, often by focusing the model on a feature within a given modality, our model classified individuals into test performance based on functional connectivity. This was performed in order to identify specific anatomical regions associated with cognitive test performance, rather than develop a diagnostic tool. Nonetheless, many studies utilizing machine learning have reported excellent performance, with accuracy, sensitivity and specificity at times exceeding 99% (Odusami et al., 2021), though a recent systematic review demonstrated a mean accuracy of 75.4% for support vector machines in predicting progression of MCI to AD (Grueso and Viejo-Sobera, 2021). However, a primary reason preventing the implementation of these models in clinical practice is their replicability, where the same models which have often overfitted to the study sample will underperform with independent data sets (Beam et al., 2020; Crowley et al., 2020). This in turn may lead to false conclusions and prevent the implementation of machine learning in settings where it may revolutionize diagnostics. It is therefore imperative that applied methodology is rigorous and validated using independent data sets.

The novelty of the machine learning technique used in this study lies in the ability to identify which features the model is relying the most on to make its prediction. This is generally difficult to do when a model has a large number of features as its input, as is the case with functional connectivity among 379 brain regions. Traditional methods would instead attempt to identify significant features prior to feeding these into a model, therefore biasing the model to focus solely on, for example, the default mode network. This however potentially removes global network information which may reveal key insights about the pathology. Our method therefore provides an embedded solution to directly analyze rsfMRI data, though further analysis techniques are necessary to identify markers from the large amount of data that results from this method.

LIMITATIONS

As stated previously, machine learning models are currently unable to determine which feature of the functional connectivity of each parcel the model uses to predict the response. The models may be highlighting either reduced activation, indicating deficits in the underlying network, or alternatively, there may be increased activity due to greater reliance on networks which are compensating, albeit ineffectively. The former may be used as markers in diagnosis and screening, whereas the latter could potentially be targeted using TMS to strengthen networks and improve symptoms, though current evidence for the therapeutic value of TMS in AD remains unclear (Weiler et al., 2020). Beyond improving computational techniques, this problem could be addressed through longitudinal studies on large

cohorts to track functional connectivity changes and connect this with clinical data and comparing these observations to neuropathological data.

Furthermore, the functional connectivity features were resolved from baseline resting-state fMRI rather than task-based fMRI. Consequently, the parcels identified by each model are not necessarily those activated when completing these tasks, but rather an association between changes in the functional connectome and the performance in each test. Finally, we did not stratify our models by diagnosis due to our limited sample size, instead favoring more stable models by opting in for classification based on best and worst performance in neuropsychiatric testing.

CONCLUSION

Diagnosing and treating AD remains one of the foremost challenges of modern medicine. We present a model of MCI and AD which provides further insight into the anatomical correlates of neuropsychological dysfunction. We demonstrate that function and dysfunction in AD is mediated by the interaction of several networks, including the DMN and CEN but also sensorimotor and visual networks. While other machine learning methods have been applied to AD with comparable performance, our machine learning model is able to peek into the black box and explain the network components contributing to models of AD directly from a whole-brain connectome. This avoids the elimination of potentially key network information which accompanies feature selection in targeted studies looking at specific networks. Focusing on whole-brain network changes in AD could potentially lead to disentangling factors contributing to a disparity between functioning individuals and those with inefficient compensation or low cognitive reserve. In turn, these insights may empower therapeutic targeting to improve disease trajectory and identify early biomarkers of disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee Shanghai Tongji Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ND, CF, and RL collected the data and drafted and edited the manuscript. WZ, ML, and WX recruited the participants and contributed to the data collection. HT, PN, OT, IY, KO, MS, and SD provided the technical assistance with the machine learning aspects of the project. MS contributed to the manuscript draft and review. YL conceived and designed framework of this study, also funded and supervised this study, and reviewed the manuscript. All authors read and approved the final manuscript.

FUNDING

This work was supported by the Database Project of Tongji University [Grant No. TJ(DB)2102], Clinical Research Project of Tongji Hospital of Tongji University [Grant No. ITJ(ZD)2002], and Shanghai Shenkang Hospital Development Center Clinical Science and Technology Innovation Project (Grant No. SHDC12021110). We gratefully acknowledge the funding support of Tongji Hospital of Tongji University and Shanghai Shenkang Hospital Development Center.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.854733/full#supplementary-material

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Conflict of Interest: HT, PN, OT, IY, KO, SD, and MS are employees of Omniscient Neurotechnology, and they provided technical assistance with the machine learning aspects of the project.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Aging Neuroscience

REVIEW
published: 27 May 2022
doi: 10.3389/fnagi.2022.834765

Cognitive Reserve and Related Constructs: A Unified Framework Across Cognitive and Brain Dimensions of Aging

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OPEN ACCESS

Edited by:
Anja Soldan, Johns Hopkins University, United States

Reviewed by:
David Bartrés-Faz, University of Barcelona, Spain
Colin Groot, Lund University, Sweden

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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *13 December 2021*
Accepted: *03 May 2022*
Published: *27 May 2022*

Citation:
Kremen WS, Elman JA, Panizzon MS, Eglit GML, Sanderson-Cimino M, Williams ME, Lyons MJ and Franz CE (2022) Cognitive Reserve and Related Constructs: A Unified Framework Across Cognitive and Brain Dimensions of Aging. Front. Aging Neurosci. 14:834765. doi: 10.3389/fnagi.2022.834765

Cognitive reserve and related constructs are valuable for aging-related research, but consistency and clarification of terms is needed as there is still no universally agreed upon nomenclature. We propose a new set of definitions for the concepts of reserve, maintenance, and resilience, and we invoke parallel concepts for each that are applicable to cognition and to brain. Our definitions of reserve and resilience correspond reasonably well to dictionary definitions of these terms. We demonstrate logical/methodological problems that arise from incongruence between commonly used conceptual and operational definitions. In our view, cognitive reserve should be defined conceptually as one's total cognitive resources at a given point in time. IQ and education are examples of common operational definitions (often referred to as proxies) of cognitive reserve. Many researchers define cognitive reserve conceptually as a property that allows for performing better than expected cognitively in the face of aging or pathology. Performing better than expected is demonstrated statistically by interactions in which the moderator is typically IQ or education. The result is an irreconcilable situation in which cognitive reserve is both the moderator and the moderation effect itself. Our proposed nomenclature resolves this logical inconsistency by defining performing better than expected as cognitive resilience. Thus, in our usage, we would test the hypothesis that high cognitive reserve confers greater cognitive resilience. Operational definitions (so-called proxies) should not conflate factors that may influence reserve—such as occupational complexity or engagement in cognitive activities—with cognitive reserve itself. Because resources may be depleted with aging or pathology, one's level of cognitive reserve may change over time and will be dependent on when assessment takes place. Therefore, in addition to cognitive reserve and cognitive resilience, we introduce maintenance of cognitive reserve as a parallel to brain maintenance. If, however, education is the measure of reserve in older adults, it

precludes assessing change or maintenance of reserve. Finally, we discuss consideration of resistance as a subcategory of resilience, reverse causation, use of residual scores to assess performing better than expected given some adverse factor, and what constitutes high vs. low cognitive reserve across different studies.

Keywords: cognitive resilience, brain resilience, cognitive reserve maintenance, peak reserve, current reserve, reverse causation

INTRODUCTION

The U.S. National Institute on Aging (NIA) sponsored the Reserve and Resilience Workshop Collaboratory led by Dr. Yaakov Stern[1]. The NIA's request for this type of workshop underscores the importance of these concepts in research on aging. Stern's work in this area has yielded very useful and highly influential constructs in aging and dementia research (Stern, 2012; Stern et al., 2020). A seminal finding that has spurred interest in cognitive reserve was Stern's observation that adults with higher educational attainment tended to have later onset of dementia, but once they did reach a point of significant cognitive impairment they then had a more rapid decline in function than those with lower education (Stern et al., 1995, 1999). The simple, yet powerful, idea is that those with more education were able to withstand more brain pathology, but having more pathology once impairment becomes manifest, they in turn may undergo a more rapid subsequent decline.

Several recent reviews and commentaries on reserve and related issues have been published (Arenaza-Urquijo and Vemuri, 2018, 2020; Cabeza et al., 2018, 2019; Montine et al., 2019; Pettigrew and Soldan, 2019; Stern et al., 2019, 2020). In April 2022, the Collaboratory's consensus framework was posted on the Collaboratory website. Indicating both foresight and openness to different perspectives, the introduction to the Collaboratory framework includes the following statements: "Our aim is to present a well-defined set of operational definitions in order to encourage, advance, and develop research on these concepts. At the same time, we want to encourage investigators who have different views or use a given concept differently to note how their definitions relate or differ with one of those described here. Similarly, this framework provides a basis for describing how the operational definition of another concept differs from those suggested here."

In keeping with that spirit, here we address what we see as some key issues, and we provide terminology that we believe is clear and can resolve some inconsistencies that are inherent in the Collaboratory's proposed framework. Many of our terms or concepts are drawn from the extant literature; some are modified, and we also suggest some new related terms. The purpose of this article is not to elucidate mechanisms that may underlie cognitive reserve and related phenomena nor to determine optimal operational definitions, although we provide several reasonable examples. Rather, our goal is simply to provide a consistent set of definitions and constructs that can be applied in efforts to examine cognitive reserve. Despite the substantial body of research on cognitive reserve and related concepts, the field still lacks clear and, most importantly, internally consistent definitions of the basic constructs that can be clearly linked to operational definitions and statistical models. We think that is an important starting point for furthering research and enhancing communication. Conceptual definitions of key terms are shown in **Box 1**. These are grouped into three major categories: Reserve, Maintenance, and Resilience. Within each category there are parallel definitions for cognition and brain.

INCONSISTENCY BETWEEN CONCEPTUAL AND OPERATIONAL DEFINITIONS

In part 1, Definition, in the Collaboratory framework (April 2022)[1], cognitive reserve is defined as "a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease." Inherent in this conceptual definition is the idea that cognitive reserve involves some sort of adaptability to aging-related changes or pathology. We consider this to be a conceptual definition which is followed by part 2, Operational Definition.

There it states that research on cognitive reserve requires three components:

(1) "measures of life course-related changes, insults, or disease or risk factors that theoretically impact cognitive outcomes; (2) measures of associated change in cognition; (3) a variable that influences the relationship between 1 and 2." An example is provided with "education as a hypothesized cognitive reserve proxy (3)", which refers to #3 above. Thus, under the Operational Definition subheading, the measure that moderates the relationship between 1 and 2 is the CR (cognitive reserve) proxy.

The following illustrates the logical disconnect, i.e., the incongruence, between the conceptual and operational definitions of cognitive reserve in this framework:

- Cognitive reserve is a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease.
- Education (or IQ) is a proxy for cognitive reserve.
- Therefore, education (or IQ) refers to a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease.

[1]https://reserveandresilience.com

BOX 1 | Conceptual definitions.

Reserve	
Cognitive reserve	An individual's total or overall cognitive resources.
Brain reserve	An individual's total neural resources or neurobiological capital.
Maintenance	
Cognitive maintenance and maintenance of cognitive reserve	The degree to which cognitive decline over time is minimized. Maintenance of cognitive reserve simply refers to maintenance with respect to cognitive reserve specifically (i.e., overall cognitive ability); it highlights the fact that cognitive reserve can change over time.
Brain maintenance	The relative absence of deterioration over time in brain structure or function.
Resilience	
Cognitive resilience	The ability to maintain cognitive performance in the face of adverse brain-related change, measured pathology, or other risk factors for cognitive decline.
Brain resilience	Brain structure or function that is better maintained given factors that cause, or increase risk for, adverse brain changes.
Resistance	Avoiding cognitive decline or brain pathology despite adverse factors. Resistance is a subcategory of resilience because resistance against one risk factor necessarily means resilience against some other factor.

Note: The distinction between maintenance and resilience depends on the presence of a measured or stated risk factor. Lack of decline in the absence of a risk factor is simply maintenance. A risk factor must be identified for there to be resilience or resistance. Thus, resilience or resistance may be viewed as the mechanism allowing for good maintenance despite the presence of a particular risk factor.

Note that the conclusion follows from the statement that education (or IQ) is a proxy for cognitive reserve. A dictionary definition of proxy is "the agency, function, or office of a deputy who acts as a substitute for another (Merriam-Webster Collegiate Dictionary[2]). Thus, we can read this statement to mean that that these are substitutes for cognitive reserve. The problem then is that the last statement about education or IQ is inaccurate. They do not, in and of themselves, indicate or measure anything about a property of the brain nor do they indicate anything about allowing for better-than-expected cognitive performance. Someone with a high IQ or high educational attainment might, for example, perform better than, worse than, or as expected. Therefore, education (or IQ) are not really substitutes for this definition of cognitive reserve. Some readers may feel that what the Collaboratory definition is really intending to say is that education (or IQ) contribute to or are associated with factors that provide the brain with properties that allow for better-than-expected performance. If so, this remains problematic for two reasons. First, it relies on intuition about the meaning of each definition. Second, it confounds the effect with factors that contribute to the effect.

Moderators vs. Moderation Effects

An interaction showing a significant moderation effect provides the strongest evidence for doing better than expected given aging- or pathology-related brain changes. For example, we might find that memory is correlated with brain pathology in a low, but not a high, education group. The terminology proposed by the Collaboratory creates the logical dilemma in which cognitive reserve (e.g., education) is simultaneously the moderator and the moderation effect itself (e.g., the education × pathology interaction on memory). Put another way, as described above, that approach confounds the effect with factors that contribute to the effect. We can think of no other research paradigm in which it would be acceptable to have the same construct be both moderator and moderation effect. One might argue that this is OK because IQ and education are really measures of adaptability since a person's total cognitive resources at a given point in time is the sum total of a dynamic process that involves the effects of genes, accumulated experiences throughout life, and adaptability. The same is true for personality traits, body mass index, and myriad other measures that change over the life course. However, despite the fact that each of these measures reflects an endpoint of a set of dynamic processes, the value of that measure only captures a single point in time and it does not necessarily indicate the possibility of better-than-expected performance.

In work that anticipated the Collaboratory, resilience is referred to as "a more general term referring to multiple reserve-related processes" such as cognitive reserve, brain reserve, and brain maintenance (Stern et al., 2020). We note this here because a key part of our resolution of the inconsistency and the blurring of the definitions of moderator and moderation effects involves a specific distinction between reserve and resilience.

RESOLVING THE INCONSISTENCY: PROPOSED DEFINITIONS

Reserve

Our proposed resolution is to conceptually define cognitive reserve as a person's total or overall cognitive resources at a given point in time. This corresponds well to a dictionary definition of reserve as "something set aside for a particular purpose, use, or reason" (Merriam-Webster Collegiate Dictionary[2]). It fits with the notion of reserves as a stockpile of resources. Brain reserve (Satz, 1993) or the similar concept of neuronal reserve (Mortimer et al., 1981) has been used to refer to the amount of premorbid brain tissue. We conceptually define brain reserve as a person's total neural resources or their neurobiological capital at a given point in time (cf. Arenaza-Urquijo and Vemuri, 2020).

Our definition of cognitive reserve is partly like that of Montine et al. (2019), who define cognitive reserve as a

[2]http://www.merriam-webster.com/dictionary

person's pre-existing or premorbid cognitive ability, i.e., their overall cognitive ability before aging- or disease-related declines. Extending their definition, we also emphasized cognitive reserve as potentially changing over the lifespan. Although we measure it operationally at a particular point in time, reserves may be augmented or depleted across the lifespan. Thus, we differentiate between prior and current level of cognitive reserve. Level and change in cognitive reserve across the lifespan are a function of the interplay of genetic predisposition and environmental influences (Stern et al., 2020). As brain development takes place, cognitive reserve tends to increase primarily early in life through young adulthood, and then tends to become depleted in later life (Zahodne et al., 2015a; Cabeza et al., 2018; Kremen et al., 2019). Importantly, older adults with the same current level of cognitive reserve could still have very different earlier or premorbid levels of cognitive reserve, and *vice versa*. Like cognitive reserve, brain reserve can change across the lifespan. In older adults, it is safe to assume that we are virtually never dealing with prior/peak brain reserve because some amount of atrophy has almost certainly taken place. Thus, we think it is important to acknowledge whether a measure is assessing current or prior reserve as studies may have more or less ability to discriminate between the two.

Given this definition of cognitive reserve, the best available indices, i.e., operational definitions, of cognitive reserve are probably IQ or other measures of general cognitive ability because these essentially measure overall cognitive resources (Boyle et al., 2021). Epidemiological studies have found that higher education is associated with reduced risk for dementia (e.g., Zhang et al., 1990; White et al., 1994; Evans et al., 1997; Beydoun et al., 2014). Subsequently, education has often been used as an operational definition of cognitive reserve. From a neuropsychological perspective, education is commonly used as a rough gauge of premorbid cognitive ability because much more precise actual premorbid cognitive test data are rarely available. Although we believe these are reasonable operational definitions, the choice should ultimately made based on the context of a given study.

In general, more extensive cognitive testing will allow for a better index of general cognitive ability. That said, we are not suggesting that that is required for studying cognitive reserve, and we recognize that extensive cognitive data may not be available, especially for indices of early or premorbid ability. Education or single cognitive measures such as vocabulary or a reading-based premorbid IQ estimate may certainly be employed as cognitive reserve measures. The strengths and limitations of any measures can then be considered. Although we are primarily thinking about cognitive reserve with respect to overall cognitive ability, it is also a valid area of investigation to examine cognitive reserve with respect to a specific cognitive domain. In that case, the index of cognitive reserve would be composed of measures tapping that specific domain as specified by the researchers. Importantly, performing better than expected is not part of our definition of cognitive reserve, although we fully agree that performing better than expected is still of central interest. As described below, our definition of resilience addresses forms of adaptability or performing better than expected.

MAINTENANCE

The concept of brain maintenance was introduced by Nyberg et al. (2012). It is the relative absence or slower rates of deterioration over time in brain structure or function. Better brain maintenance is simply minimizing deterioration over time, often measured by cortical thinning or volume reductions. As such, this concept does not necessarily apply to childhood and adolescence when brain development, rather than maintenance, is considered optimal. Although weaker inferences may be drawn from cross-sectional findings that are consistent with brain maintenance, longitudinal assessment is necessary to be able to truly determine brain maintenance (see below).

Cognitive Maintenance and Maintenance of Cognitive Reserve

Here we introduce new terms that parallel Nyberg et al.'s (2012) concept of brain maintenance: cognitive maintenance and maintenance of cognitive reserve. We define cognitive maintenance as the degree to which cognitive decline over time is minimized. We generally use the term cognitive maintenance in regard to measures of specific cognitive abilities. When applied to measures of overall cognitive ability, it may be conceptualized as maintenance of cognitive reserve. In this sense, equivalent prior/premorbid and current cognitive reserve would indicate strong cognitive reserve maintenance. Better cognitive maintenance simply refers to observed lack of decline and can thus be used even when no measures of pathology or other adverse factors are available.

Like brain maintenance, cognitive maintenance (or maintenance of cognitive reserve) really requires longitudinal assessment. In a statistical model, baseline or peak cognitive reserve corresponds to the intercept and cognitive reserve maintenance corresponds to the slope. If two people have high and low prior cognitive reserve, respectively, it may the case that they decline at similar rates, i.e., they have different intercepts but parallel slopes or trajectories. Thus, they would have equivalent cognitive reserve maintenance, but the one who began with a lower intercept will reach the threshold for cognitive impairment or dementia earlier. This scenario has been aptly termed "preserved differentiation" by Salthouse et al. (1990). If the slopes are different and one individual has steeper declines, as tested with an interaction effect, that would indicate a differential cognitive maintenance (i.e., better cognitive maintenance corresponds to a more positive or less negative slope). In the terminology of Salthouse et al. (1990), this scenario has been termed "differential preservation." Salthouse's terminology applies equally to maintenance of specific cognitive abilities or maintenance of cognitive reserve.

Using this approach, we previously showed that after controlling for midlife cognitive reserve level, there was still some advantage with respect to specific cognitive abilities in having high cognitive reserve in young adulthood (Eglit et al., 2022). Although declines are usually associated with poorer outcomes, despite being essentially equated for current cognitive reserve, this high declining group performed better on specific cognitive

abilities in mid- and later life. We referred to this as a paradoxical reserve phenomenon because of the advantages shown in the declining group.

We suspect that a major reason for the lack of reference to maintenance of cognitive reserve in the literature is due to education and reading-based premorbid IQ estimates being the most common indices of cognitive reserve. In studies of older adults, it is not possible to examine change in reserve based on these indices.

RESILIENCE

Resilience is a generic term that could be applied to cognition, brain, depression and many other constructs. In keeping with our effort to define parallel terms for cognition and brain, we think it is important to specify cognitive or brain resilience. We define cognitive resilience as the ability to maintain cognitive performance in the face of adverse brain-related change, measured pathology, or other risk factors for cognitive decline. Like our definition of cognitive reserve, this corresponds to a dictionary definition of resilience as "the ability to recover from or adjust easily to misfortune or change" (Merriam-Webster Collegiate Dictionary[2]).

Inferring cognitive resilience requires some adverse change or factor that a person can be resilient against. Thus, cognitive maintenance in the absence of any known or specified adverse factor would not come under the rubric of resilience. Cognitive performance might, for example, be resilient against Alzheimer's disease pathology (amyloid and tau) or neurodegeneration. Carrying the *APOE*-ε4 allele or experiencing environmental exposures such as air pollution, which can also have adverse brain effects, are examples of additional factors one may be resilient against. In a statistical model, these types of cognitive resilience would be operationally defined as interaction effects (e.g., that young adult cognitive reserve moderates the association between pathology and current cognitive performance, or that among *APOE*-ε4 carriers, young adult cognitive reserve moderates the association between medial temporal lobe volume and episodic memory).

Figure 1 depicts the relationship between cognitive reserve and resilience in our framework. The figure provides three examples of longitudinal scenarios. Our proposed terminology is applicable to cross-sectional studies as well, but we recommend that findings from cross-sectional data are framed as "consistent with" resilience rather than definitive evidence. Baseline in each panel refers to the earliest point at which cognitive reserve is measured in a given study. Each panel is consistent with normative decline, i.e., the most common scenario of depletion of cognitive reserve with advanced aging (cf. Zahodne et al., 2015a). **Figure 1A** depicts an advantage of higher cognitive reserve that is present at baseline and remains constant over time with no evidence of resilience. This is what Salthouse referred to as preserved differentiation. **Figure 1B** depicts a situation in which two groups have equivalent baseline cognitive reserve. Assuming some pathological factor, the orange group exhibits greater cognitive resilience because they have less cognitive decline (alternatively, better maintenance of cognitive reserve). **Figure 1C** depicts a case in which one group has both greater baseline cognitive reserve and greater cognitive resilience (alternatively, better maintenance of cognitive reserve). In Salthouse's terminology, **Figure 1B** would be an example of differential preservation and **Figure 1C** could arguably show both differential preservation and preserved differentiation. Because the less steep slope in **Figures 1B,C** implies performance that is better than expected, it corresponds to the final April 2022 Collaboratory framework definition of cognitive reserve. In contrast to our usage, resilience is a general, overarching term in the Collaboratory framework (Stern et al., 2020), so there is no real differentiation between reserve and resilience. But with that definition of cognitive reserve, it no longer seems relevant for later life interventions to improve cognitive function because it is important to differentiate whether the effects of interventions are on reserve or resilience. In this case, the orange lines would represent the group undergoing the intervention. Individuals participating in cognitive training and their families are most likely to want to know whether it will boost their cognitive resilience (i.e., slower rate of decline compared to no intervention) rather than simply boost cognitive reserve (i.e., baseline post-intervention functioning higher than pre-intervention) with no impact on rate of decline.

Directly paralleling our conceptualization of cognitive resilience, we define brain resilience as brain structure or function/activation that is better maintained given factors that cause, or increase risk for, adverse brain changes. Evidence of brain resilience thus requires evidence of these deleterious factors. Examples of brain resilience might be evidence of higher-than-expected hippocampal volume given *APOE*-ε4 homozygosity or pathological levels of beta-amyloid.

Because cognition arises from brain, cognitive resilience must ultimately be due to brain resilience. Thus, it does not seem possible for the two to be entirely independent, i.e., to have cognitive resilience without brain resilience. On the other hand, different scenarios are conceivable. If we examine amyloid accumulation as a type of brain pathology, then brain resilience might be manifest by reduced hippocampal atrophy over time. Trajectories of episodic memory decline that are less steep than trajectories of hippocampal atrophy would additionally constitute cognitive resilience. However, if the trajectory of episodic memory decline always parallels that of hippocampal atrophy, that would not represent cognitive resilience. In the latter case, cognitive performance is not better than expected given the level of brain resilience.

Arenaza-Urquijo et al. (2017) and Arenaza-Urquijo and Vemuri (2020) have proposed that aging and dementia research will benefit from a distinction between resilience and resistance. Like their definition, we define resistance as avoiding pathology or cognitive decline despite the existence of some adverse factor. A risk factor must be identified for there to be resilience or resistance. In the absence of a risk factor (or if a risk factor is not specified), manifesting good performance or the lack of decline or pathology is simply maintenance. We consider resistance to be a subtype of resilience because it is not possible to be resistant without being resilient against something else. Which term is applicable may simply depend on whether one is looking

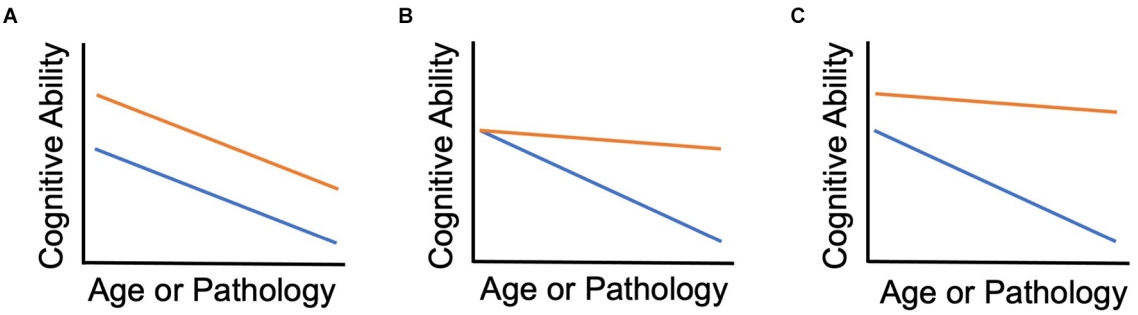

FIGURE 1 | Cognitive reserve and cognitive resilience. **(A)** Orange group has higher reserve but no difference in resilience. **(B)** Baseline reserve is equal between groups; Orange group shows resilience over time compared to the blue group. **(C)** Orange group has both higher baseline reserve and shows resilience over time.

"upstream" or "downstream." If someone has low amyloid levels despite being *APOE*-ε4 homozygous, then they are resistant to amyloid accumulation but they are—by definition—also resilient against their high genetic risk.

IMPLEMENTATION IN RESEARCH

Two examples illustrate how our proposed usage can be applied in empirical research and how it avoids conflating moderator and moderation effects. We previously showed that the association between hippocampal volume and episodic memory was moderated by young adult general cognitive ability, i.e., young adult cognitive reserve (Vuoksimaa et al., 2013). Memory performance and hippocampal volume were positively correlated in the lower reserve group, but not in the higher reserve group. The results are consistent with the idea that higher cognitive reserve is protective against the effects of hippocampal atrophy, so that memory in those with high reserve was less dependent on hippocampal volume. In 2013, we referred to both young adult general cognitive ability and the moderation effect as cognitive reserve. In our current proposed usage, we would say that higher cognitive reserve appeared to confer greater cognitive resilience in the face of smaller hippocampal volume. In another study, we showed that the same young adult measure of cognitive reserve moderated the association between midlife lifestyle and later brain aging (Franz et al., 2021). Favorable lifestyles were associated with less advanced brain aging among individuals with lower young adult cognitive reserve, but individuals with higher young adult cognitive reserve had less advanced brain aging regardless of lifestyle. In this case, we concluded that higher young adult cognitive reserve conferred cognitive resilience against the adverse effects an unfavorable lifestyle on brain aging. In addition, we concluded that a favorable lifestyle conferred resistance to advanced brain aging because it was associated with little advanced brain aging. This result might also reflect brain maintenance, but we were reluctant to make that inference because brain age was measured at only a single time point.

Parallel Concepts for Cognition and Brain

Some researchers argue that we should use a single term for reserve without differentiating between cognitive and brain reserve because all cognition arises from the brain (Cabeza et al., 2018). Others, however, argue that it is important to distinguish between the two (Stern et al., 2020). Although the former raises a valid conceptual point, we agree with the latter position for practical reasons. It is, of course, true that cognition arises from the brain, but people with very similar brain pathology may have vastly different levels of cognitive function, and those with similar cognitive function may have very different brains. Indeed, studies reviewed by Cabeza and colleagues indicate that the same cognitive performance has been associated with different patterns of brain activity in younger and older adults (Dolcos et al., 2002). In our view, this lack of one-to-one correspondence between brain and cognition suggests that it is useful to retain separate terms for cognitive reserve and brain reserve. With continued advancement in mapping the brain, that correspondence may become closer. As a result, the importance of brain reserve might increase relative to that of cognitive reserve.

Some researchers may suggest that brain structure captures brain reserve whereas brain function/activation captures cognitive reserve. A brain activation pattern (e.g., as observed in fMRI) that is linked to overall cognitive ability may serve to elucidate mechanisms underlying cognitive reserve, but in our view, it would not be considered to operationally define cognitive reserve because the functional brain activation pattern itself is not cognition. Similarly, we can assume that some particular pattern of brain activation involving motor, memory, and association areas underlies performance of a pirouette in ballet, but we would not want to define that brain activation pattern as a pirouette.

Issues Regarding Cognitive Reserve Proxies

In commentaries on reserve (Cabeza et al., 2018; Stern et al., 2020), it is stated that reserve is a construct or concept that cannot be measured directly and can only be measured *via* proxies. Personality is assessed with a variety of personality inventories. Memory may be assessed by story or list recall. Personality, memory, intelligence, and myriad others are theoretical or latent constructs that cannot be measured directly. In our view, referring to operational definitions of cognitive reserve as proxies tends to convey that cognitive reserve is somehow

different—more cryptic and more difficult to measure—than other behavioral or psychological constructs. If the proxy is actually a substitute for the construct (as number of words recalled from a list is a substitute for the construct of episodic memory), then use of the term would not be problematic. Of course, it could then simply be referred to as the operational definition in line with conventional scientific usage. However, as explained through our syllogism example, the so-called proxies do not constitute substitutes for cognitive reserve as defined by the Collaboratory. The term proxy does not get around the inconsistencies we have noted between operational and conceptual definitions of reserve. This holds true whether the so-called proxy is a cognitive measure (e.g., vocabulary) or a lifestyle measure (e.g., engagement in cognitive activities). The importance of considering how an operational measure is related to conceptual definitions is discussed in the next section.

Differentiating Cognitive Reserve From Factors That May Influence Cognitive Reserve or Resilience

We are concerned regarding what we see as dilution of the concept of cognitive reserve. Cognitive reserve is determined by genetic factors plus accumulated experiential factors that may tend to enhance or reduce the level of reserve. Experiential/environmental factors might, for example, include nutrition, physical activity, exposure to education, exposure to air pollution, occupational complexity, and engagement in cognitively stimulating activities. These measures—individually or in composite indices—have often been used as so-called proxies for cognitive reserve. Even socioeconomic status has sometimes been included in measures of cognitive reserve. We strongly argue against this practice. These measures may contribute to one's cognitive reserve (i.e., their overall cognitive capacity), or cognitive resilience (i.e., better-than-expected performance), or they could be the product of cognitive reserve. But they are not measures of cognitive resources or capacity, nor do they say anything in and of themselves about better-than-expected performance. Low physical activity, for example, may contribute to obesity, but it makes no sense to suggest it as a proxy (substitute) for obesity. These other measures may be included in data analytic models, as variables that may affect cognitive reserve or be partially driven by cognitive reserve rather than as indices of cognitive reserve themselves. The way in which a given measure may be related to reserve should simply be described (e.g., "measure X contributes to reserve" or "measure X is the product of high reserve"). This distinction is also important because factors that contribute to cognitive reserve may represent potential targets for intervention. Finally, including socioeconomic status as part of a cognitive reserve measure is particularly problematic given the potential implication that simply being poor means one has low cognitive reserve.

We make an exception for education as an indicator of cognitive reserve—even though it is not a direct measure of cognitive ability—because people with greater cognitive capacity tend to attain higher levels of education. Because early cognitive data are rarely available, it is traditional in neuropsychological assessment to use education as a rough way to gauge a person's expected level of cognitive function. Consequently, education is often used to estimate peak cognitive reserve. That said, it is worth noting that education is a rather crude index of cognitive reserve. With that in mind, we showed that a measure of general cognitive ability taken during young adulthood, but not education, moderated the correlation between memory and hippocampal volume (Vuoksimaa et al., 2013). A similar finding has subsequently been shown for current verbal intelligence compared with education (Boyle et al., 2021).

Cognitive Reserve and the Question of Reverse Causation

A key drawback of using variables other than direct cognitive measures—including education—as indicators of cognitive reserve is the "chicken-egg" problem. We referred to factors that *may* influence reserve in order to avoid assumptions about direction of effect. For example, does engaging in cognitively stimulating activities reduce age-related declines or is it that individuals with higher cognitive reserve tend to engage more in cognitive-related activities? Does getting more education increase one's cognitive reserve or do people with more cognitive reserve tend to attain higher levels of education? There is evidence that during childhood and adolescence—when there is substantial brain development—that education provides an environment that promotes increases in IQ or general cognitive ability (Ritchie and Tucker-Drob, 2018). However, that effect appears to level off by young adulthood (Kremen et al., 2019). We have shown, for example, that after accounting for a direct measure of general cognitive ability administered in young adulthood, education, occupational complexity, and engaging in cognitive activities later in life accounted for less than 1% of the variance in later cognitive function (Kremen et al., 2019). These results are consistent with reverse causation, i.e., that the impact of education, occupational complexity, and cognitive activities *after early adulthood* was not truly causal.

The possibility of reverse causation receives far too little attention in studies of cognitive reserve. This possibility is another reason to avoid considering measures such as engagement in leisure activities or occupational complexity to be indices of cognitive reserve. For example, engaging in leisure activities might enhance cognitive reserve, which in turn may enhance cognitive resilience. However, higher cognitive reserve may make someone more inclined to engage in leisure activities, so leisure activities may be associated with cognitive resilience due to reverse causation. Alternatively, both could independently be associated with cognitive resilience. Using leisure activities as a proxy or measure of cognitive reserve or including it in a composite reserve measure precludes examining these possibilities.

To be able to infer causal effects of educational or cognitively stimulating exposures later in life and avoid the problem of reverse causation, individuals must be randomly assigned to conditions. With random assignment, cognitive training programs of various kinds have shown some modest improvements in cognitive function and/or brain structure

(Willis et al., 2006; Hertzog et al., 2008; Park et al., 2014; Carlson et al., 2015; McDonough et al., 2015; Motes et al., 2017). Consistent with our conclusion that young adult cognitive ability is the primary driver, the successful training programs have tended to involve intensive and lengthy training with relatively small effects. However, if those effects help to slow decline, they may be well worth it.

Considerations for the Use of Residual Scores

In some cases, researchers may wish to examine residual scores to determine if cognitive function is better or worse than expected given some indices of their brain status or some adverse risk factor. Studies of cognitive reserve and resilience using this approach have been subjected to a meta-analysis by Bocancea et al. (2021). An example of this approach would be regressing memory performance on level of beta-amyloid. A positive residual score indicates that the observed memory score is higher than the score predicted by the regression equation. A negative residual indicates lower than expected performance. Although this may be labeled as higher and lower cognitive reserve, we note that under our terminology it would more closely reflect cognitive resilience. However, if the measures do not necessarily indicate adverse factors (e.g., cross-sectionally measured hippocampal volume without evidence of atrophy), then it does not provide strong evidence of resilience.

Critically, the use of residual scores to assess resilience is dependent on the association between the predictor and outcome variables (Elman et al., 2022). For this approach to be meaningful, the magnitude of the correlation between the relevant variables (e.g., brain structure and memory) must be relatively high. If these measures are only modestly correlated, as is often the case when correlating cognitive scores with MRI measures of brain structure or measures of pathology, then the residual memory score will be very highly correlated with original memory score. As such, the residual score may provide little or no predictive value that is not already provided by the original memory score. This is true for change in residual scores over time vs. change in original scores over time.

Longitudinally, one could also compare observed vs. predicted memory scores at time 2 given one's memory at time 1. One could then examine whether lesser or greater than expected decline based on residual scores was predictive of future outcomes. However, because those with greater than expected decline will also tend to have lower scores at time 2, it is important to test whether the residual score is significant over and above the person's score at time 2 (Kremen et al., 1998; Franz et al., 2019). Essentially, this addresses the question of which is the primary determinant: how the person got there (i.e., their trajectory) or where they are at currently?

What Constitutes High or Low Cognitive Reserve?

Within a given study of cognitive reserve, it is common to classify individuals as low or high reserve. Those classifications are typically made relative to others within a particular study sample and may have little comparability across different studies. What constitutes low reserve may be particularly important for Alzheimer's-related studies. Several major studies of Alzheimer's disease comprise older adults whose average education is very high relative to their cohort in the population. Consider, for example, a study that began in 2005 with an average baseline age of 72 and average education of approximately 16 years. The average birth year would be 1933. U.S. census data show how highly atypical this educational level is in that only about 10% of that cohort attained a 4-year college degree (Ryan and Bauman, 2016). This issue has significant implications for the study of Alzheimer's disease given that low education—the most commonly used index of cognitive reserve—is associated with increased risk for dementia.

The relevance of defining low and high cognitive reserve is illustrated with data from four studies in which participants were divided into high and low reserve groups. In the study of Yaffe et al. (2011), there were two indices of cognitive reserve. One index defined low reserve (55% of the sample) as less than a high school education. The other index defined low reserve (15% of the sample) as literacy at or below the sixth-grade level. The sample of Soldan et al. (2017) had a mean education level of 17.0 (SD = 2.4; Soldan et al., 2017). The high and low cognitive reserve group in the sample of Vuoksimaa et al. (2013) had 14.9 (SD = 2.6) and 12.9 (SD = 1.9) years, respectively. Zahodne et al. (2015b) had a high education group with 9–20 years and a low education group with 0–8 years of education (Zahodne et al., 2015b). What would be the high reserve group in the studies of Yaffe et al. or Zahodne et al. would cover both groups in the study of Vuoksimaa et al. Being two SDs below the mean in the study of Soldan et al. (2017) would correspond to about the middle of the low reserve group in the study of Vuoksimaa et al. (2013) and would place someone solidly within what would be the high reserve group in the studies of Yaffe et al. and Zahodne et al. These were well-designed studies, but they highlight the fact that the meaning of high and low reserve may be radically different across studies. As such, the inferences we make about such comparisons may not translate well from one study to another. More attention should thus be paid to this issue when comparing results across studies. Because indices of cognitive reserve often do not have a standardized scale, the correspondence of high and low reserve across studies should be addressed when comparing results across studies.

SUMMARY AND CONCLUSIONS

Cognitive reserve and related constructs have proven to be valuable tools for aging-related research, but we believe greater consistency in the definition of terms both within and between studies is still needed to improve communication. Greater clarification in the definition of terms should also improve study design and inferences made on the basis of study results. Key points regarding these concepts and definitions are as follows: (1) cognitive reserve can be defined as overall cognitive resources *at a given point in time*; (2) as such, we suggest that prior/peak vs. current cognitive reserve be specified; (3) like brain maintenance, cognitive (reserve) maintenance is a dynamic process that must

be evaluated longitudinally; (4) cognitive resilience is evidence of a dynamic process that involves maintaining performance in the face of pathology or some other adverse factor; (5) resistance can be viewed as a subcategory of resilience because resistance against some downstream adverse factor necessarily implies resilience against some upstream factor; (6) given our current knowledge and measurement ability, it is useful for researchers to have parallel terms for each of these applying to brain and cognition; (7) it is important to clearly differentiate between reserve and factors that may influence reserve; (8) greater attention to the possibility of reverse causation is warranted; (9) greater caution is warranted in making causal inferences about these phenomena in cross-sectional studies; (10) attention to the definitions of low and high cognitive reserve within studies will be important to enhance our ability to compare results across studies.

We believe our terminology lends itself to a clear analytic framework, eliminates confusion, avoids logical inconsistency between conceptual and operational definitions, and clearly differentiates between moderator and moderation effects. The next steps will be to identify the specific underlying process or mechanism that accounts for higher cognitive reserve conferring greater resilience.

AUTHOR CONTRIBUTIONS

WK, JE, MP, GE, and CF contributed to the conception and design of the manuscript. WK wrote the first draft of the manuscript. WK, JE, MP, GE, and CF wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by National Institutes of Health; National Institute on Aging (R01s, AG050595, AG022381, AG054002, AG054509, AG060470, AG062483, K01 AG063805, and P01 AG055367) and the National Center for Advancing Translational Science (CTSA grant KL2TR001444). The Cooperative Studies Program of the U.S. Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry. The content is the responsibility of the authors and does not necessarily represent official views of the NIA, NIH, or VA.

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MINI REVIEW
published: 19 July 2022
doi: 10.3389/fnagi.2022.903269

Neural Networks in Autosomal Dominant Alzheimer's Disease: Insights From Functional Magnetic Resonance Imaging Studies

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Alzheimer's disease (AD) is the most common form of dementia, with no cure to stop its progression. Early detection, diagnosis, and intervention have become the hot spots in AD research. The long asymptomatic and slightly symptomatic phases of autosomal dominant AD (ADAD) allow studies to explore early biomarkers and the underlying pathophysiological changes. Functional magnetic resonance imaging (fMRI) provides a method to detect abnormal patterns of brain activity and functional connectivity *in vivo*, which correlates with cognitive decline earlier than structural changes and more strongly than amyloid deposition. Here, we will provide a brief overview of the network-level findings in ADAD in fMRI studies. In general, abnormalities in brain activity were mainly found in the hippocampus, the medial temporal lobe (MTL), the posterior cortex, the cingulate cortices, and the frontal regions in ADAD. Moreover, ADAD and sporadic AD (SAD) have similar fMRI changes, but not with aging.

Keywords: autosomal dominant Alzheimer's disease, neural network, functional MRI (fMRI), presenilin, amyloid precursor protein (APP)

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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *14 April 2022*
Accepted: *03 June 2022*
Published: *19 July 2022*

Citation:
Qiu Q (2022) Neural Networks in Autosomal Dominant Alzheimer's Disease: Insights From Functional Magnetic Resonance Imaging Studies. Front. Aging Neurosci. 14:903269. doi: 10.3389/fnagi.2022.903269

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the progressive loss of cognitive function and independence, with extracellular plaque deposits of the β-amyloid peptide (Aβ) and flame-shaped neurofibrillary tangles of the microtubule-binding protein tau. Autosomal dominant AD (ADAD) accounts for less than 1% of all AD cases (Bekris et al., 2010), which is attributed to mutations in three genes: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*). Mutation carriers usually develop dementia at an early age (about 30 to 50 years of age), while sporadic AD (SAD) subjects develop symptoms of progressive amnesia and other cortical cognitive symptoms, usually after age 60. With mutation-specific exceptions and an earlier age of onset, ADAD is similar to SAD. Owing to the nearly 100% penetrance of ADAD, it is possible to identify early biomarkers and explore the initial pathophysiological mechanisms in cognitively unimpaired ADAD mutation carriers. Furthermore, studies that recruit subjects in presenile, mild-adulthood, or even childhood can reduce the impact of aging and other comorbidities on the results of functional magnetic resonance imaging (fMRI) research.

Functional magnetic resonance imaging is a technique for measuring and mapping brain activity and functional connectivity. It can be conducted in the resting state (rs-fMRI) or during the performance of particular cognitive tasks (task-related fMRI), which allows the assessment of

intrinsic activity and polysynaptic connections in the brain. Task-based and resting-state represent the two most common experimental paradigms of functional neuroimaging. Task-related fMRI is model-driven and rs-fMRI analysis is data-driven. They can reflect different features of functional changes in the brain. By comparing the differences in the activation areas of different groups on the task, topics such as disease, development, and cognition can be analyzed. The rs-fMRI analysis is data-driven, and its analytical approach focuses on describing the synergistic and spontaneous activity of the brain. Blood oxygenation level-dependent (BOLD) imaging is the standard technique used to generate images in fMRI studies and relies on regional differences in cerebral blood flow to delineate regional activity. Functional connectivity matrices and hub nodes (central positions of brain information transmission) are typically used for fMRI data analysis. Growing evidence suggests that spontaneous activity of interregional neural synchrony has a coherent structure and may play a role in a host of cognitive and neural processes. Brain functional changes may accompany or even precede detectable structural alterations (Nakamura et al., 2017; Anckaerts et al., 2019), and brain activity and functional connectivity are more consistent with cognitive function than structural imaging and amyloid deposition (Jann et al., 2020; Reas et al., 2020). Thus, exploring the functional changes in ADAD is useful for identifying early biomarkers and potential circuit-based therapeutic targets. fMRI studies have been widely demonstrated in aging (Sala-Llonch et al., 2015; Chen, 2019), late-onset AD (LOAD) (Dickerson and Sperling, 2009; Vemuri et al., 2012), and many other neurodegenerative disorders (Chen, 2019), whereas ADAD-related fMRI studies are relatively insufficient. We will review brain functional changes and potential targets in ADAD based on task-related and resting-state fMRI studies. We systematically searched studies from MEDLINE (The National Library of Medicine), Web of Science, EMBASE, and Cochrane Library inception through 31 December 2021. The characteristics of studies investigating fMRI changes in ADAD are briefly summarized in **Table 1**.

TASK-RELATED NEURAL NETWORKS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE

Task-related fMRI can be used to study brain activity when a subject is engaged in a given task. Loss of memory, an early and prominent symptom in patients with AD, correlates with parameters of structural or functional brain integrity. Memory tasks are the most widely used in ADAD fMRI studies. The selection of specific neural networks and abnormalities found in fMRI studies depend heavily on the types of memory or behavior tasks engaged. Despite this, the medial temporal lobe (MTL) (Mondadori et al., 2006; Quiroz et al., 2010, 2015; Braskie et al., 2012, 2013; Reiman et al., 2012) has been demonstrated to be selectively impaired in ADAD along with the posterior cingulate cortex (PCC) (Sala-Llonch et al., 2013; Quiroz et al., 2015) which are also regions of early structural and F-18 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) biomarkers in ADAD.

A pioneering fMRI study on ADAD related to memory tasks reported only two mutation carriers (*PSEN1* C410Y) (Mondadori et al., 2006). The 20-year-old mutation carrier displayed enhanced brain activity in the left frontal, the temporal, and the parietal neocortices, while activity levels of the 45-year-old mutation carrier were generally low in many left and right hippocampal segments during episodic memory tasks, but not working memory. Increased activity in the middle temporal gyri and the fusiform was also demonstrated during the novelty encoding tasks in other research, as the subjects approached the estimated age of onset (Braskie et al., 2013). The estimated age of onset means that people who carry a familial Alzheimer's gene tend to develop symptoms at around the same age. This helps researchers predict their disease stage and select participants for clinical trials. Increased activity may be partially explained by neuro hypertrophy, neuroinflammation, and fiber sprouting during the compensatory stage of pathophysiology (Hashimoto and Masliah, 2004; Stern et al., 2004; Sperling et al., 2010; Zott et al., 2018). These studies suggest that increased fMRI activity in the temporal lobe may be related to incipient ADAD processes, and episodic memory tasks may potentially be manageable to provoke brain activity in the pre-clinical phase of AD (the stage occurring before a clinical diagnosis of a cognitive disorder). The studies have also shown decreased activity of the temporal region in cognitively unimpaired ADAD mutation carriers. In the verbal paired-associate task fMRI study, pre-symptomatic mutation carriers showed less fMRI activity in the hippocampus and the posterior middle temporal gyrus than controls during retrieval (Braskie et al., 2013). This may be due to the different tasks or the older age of the participants in the latter study. Overall, the hippocampus, the middle temporal gyri, the fusiform, and the middle temporal gyri presented early activity changes in fMRI in subjects at risk for ADAD. It has been reported that the hippocampus can interact with the fusiform gyrus to participate in cognitive networks. Activation in the hippocampus may be related to the novelty of the stimulus, while the fusiform gyrus has been proven to be important in novelty encoding (Yamaguchi et al., 2004), object processing (Tyler et al., 2004), and recognition of complex visual stimuli (Stern et al., 1996).

As for the PCC and parietal region, asymptomatic mutation carriers showed increased BOLD activity in the posterior cingulate and symptomatic mutations carriers showed increased activity in the lingual gyrus, with precuneus cortex activity increased in both the asymptomatic and symptomatic mutation carriers during the visual memory encoding task, compared to non-mutation carriers (Sala-Llonch et al., 2013). In a verbal paired-associate task-related fMRI study, less signal in the inferior parietal cortex and the precuneus during retrieval, not encoding, was found in pre-symptomatic mutation carriers. Even after controlling for gray matter volume as a covariate, there were still significant differences in these regions, which indicated that atrophy could not explain the entire effect (Braskie et al., 2013). The PCC, precuneus, and parietal cortex are involved in many cognitive functions, including episodic memory, working memory, the focus of attention, visuospatial processing, etc.

TABLE 1 | Characteristics of studies investigating functional magnetic resonance imaging (fMRI) changes in autosomal dominant Alzheimer's disease (ADAD).

Category	References	Mutated genes involved	Subjects	Ages of mutation carriers (years)	Cognition status of participants	fMRI tasks used/methods of functional connectivity analysis	Mainly affected brain regions	Publication year
Task-related neural networks	Mondadori C. R. A. THER et al. (Sala-Llonch et al., 2015)	*PSEN1* C410Y	*N* = 1	20	preclinical stage	face-profession for episodic memory and working memory	enhanced brain activity in left frontal, temporal, and parietal neocortices during learning, retrieval, and novelty detection	2006
	Mondadori C.R.A. et al. (Sala-Llonch et al., 2015)	*PSEN1* C410Y	*N* = 1	45	aMCI	face-profession for episodic memory and working memory	significantly weaker MTL activity as well as many areas of weaker neocortical activity	2006
	Quiroz Y.T. et al. (Chen, 2019)	*PSEN1* E280A	N (mutation carriers) = 20; N (mutation non-carriers) = 19	Mean age ± SD = 33.70 ± 6.01	preclinical stage	face-name paired-associate learning task	Increased activation of the right anterior hippocampus during encoding of novel face-name associations	2010
	Ringman J.M. et al. (Johnson et al., 1998)	*PSEN1* A431E, *PSEN1* L235V, *APP* V717I	N (mutation carriers) = 11; N (mutation non-carriers) = 7	Mean age (range): 29.9 (23 to 43)	preclinical stage	novelty encoding task	decreased BOLD signal in the anterior cingulate gyrus bilaterally and the left frontal pole during a novelty encoding task	2011
	Reiman E.M. et al. (Dickerson and Sperling, 2009)	*PSEN1* E280A	N (mutation carriers) = 20; N (mutation non-carriers) = 24	Mean age ± SD = 22 ± 3	preclinical stage	face-name associative memory encoding and novel viewing and control tasks	significantly greater activation in hippocampal and parahippocampal regions and less deactivation in precuneus and posterior cingulate regions	2012
	Braskie M. N. et al. (Vemuri et al., 2012)	*PSEN1* A431E, *PSEN1* L235V, *APP* V717I	N (mutation carriers) = 18; N (mutation non-carriers) = 8	Mean age (range): 30.9 (19 to 43)	preclinical period to MCI stage	novelty encoding task	no significant difference in fMRI activity between mutation carriers and non-carriers; greater fMRI activity in the fusiform and middle temporal gyri when approaching the familial age of disease diagnosis	2012
	Braskie M. N. et al. (Mondadori et al., 2006)	*PSEN1* A431E, *PSEN1* L235V, *APP* V717I	N (mutation carriers) = 9; N (mutation non-carriers) = 8	Mean age ± SD = 29.8 ± 5.6	preclinical stage	verbal paired associates task	less fMRI activity in the left hippocampus during memory retrieval	2013
	Sala-Llonch R. et al. (Reiman et al., 2012)	*PSEN1* mutations (M139T, K239N, L235R, L282R, L286P, I439S)	N (mutation carriers) = 19; N (mutation non-carriers) = 13	AMC: Mean age ± SD = 39.09 ± 10.74; SMC: Mean age ± SD = 48.91 ± 7.53	preclinical period to dementia stage	visual encoding task	SMC showed reduced activity in regions of the left occipital and left prefrontal cortices, while both AMC and SMC showed increased activity in a region within the precuneus/posterior cingulate	2013

(Continued)

TABLE 1 | (Continued)

Category	References	Mutated genes involved	Subjects	Ages of mutation carriers (years)	Cognition status of participants	fMRI tasks used/methods of functional connectivity analysis	Mainly affected brain regions	Publication year
	Quiroz Y.T. et al. (Quiroz et al., 2010)	*PSEN1* E280A	N (mutation carriers) = 18; N (mutation non-carriers) = 19	Mean age ± SD = 13 ± 2	preclinical stage	face-name associative encoding task	less fMRI deactivation of posterior parietal regions during a memory encoding task	2015
Resting-state networks	Chhatwal J.F et al. (Cera et al., 2019)	*PSEN1*: 68, *PSEN2*: 5, *APP*: 10	N (mutation carriers) = 83; N (mutation non-carriers) = 37	AMC: Mean age ± SD = 34.64 ± 8.04; early SMC: Mean age ± SD = 44.46 ± 11.74; SMC with dementia: Mean age ± SD = 49.33 ± 9.72	preclinical period to dementia stage	independent component analysis	significantly decreased DMN fcMRI in the precuneus/posterior cingulate and parietal cortices	2013
	Sala-Llonch R. et al. (Reiman et al., 2012)	*PSEN1* mutations (M139T, K239N, L235R, L282R, L286P, I439S)	N (mutation carriers) = 19; N (mutation non-carriers) = 13	AMC: Mean age ± SD = 39.09 ± 10.74; SMC: Mean age ± SD = 48.91 ± 7.53	preclinical period to dementia stage	seed-based correlation analysis	increased frontal connectivity and reduced posterior connectivity in AMC and decreased frontal and increased posterior connectivity in SMC	2013
	Thomas J.B. et al. (Buckner, 2012)	mutations not identified in the text	N (mutation carriers) = 54; N (mutation non-carriers) = 25	CDR = 0: Mean age ± SD = 33.9 ± 8.5; CDR = 0.5: Mean age ± SD = 41.4 ± 10.4; CDR ≥ 1: Mean age ± SD = 49.4 ± 8.7	preclinical period to MCI stage	seed-based correlation analysis	lower functional connectivity in multiple resting-state networks in asymptomatic mutation carriers near anticipated age of symptom onset; largely similar functional connectivity changes owing to advanced AD in LOAD and ADAD	2014
	Quiroz Y.T. et al. (Quiroz et al., 2010)	*PSEN1* E280A	N (mutation carriers) = 18; N (mutation non-carriers) = 19	Mean age ± SD = 13 ± 2	preclinical period	seed-based correlation analysis	no differences in functional connectivity in the whole network metric	2015
	Zhao T. et al. (Acosta-Baena et al., 2011)	*PSEN1*: 16, *PSEN2*: 1, *APP*: 9	N (mutation carriers) = 26; N (mutation non-carriers) = 29	Mean age ± SD = 33.65 ± 4.43	preclinical period	seed-based correlation analysis	decreased connectivity of left precuneus with right precuneus and superior frontal gyrus and decreased connectivity of medial frontal gyrus with middle frontal gyrus	2020
	Quan M. et al. (Moussa et al., 2012)	*PSEN1* mutations (H163R, L282V, L392V, M270L, L271V, M139V, M139L, I213T, A285V, F105I, I100F, K311R, P433S, G111V, L173F, G206S), *PSEN2* (F181I, V214L, M298T, G34S), and *APP* (I716T, V717I, V715M)	N (mutation carriers) = 70; N (mutation non-carriers) = 102	AMC: Mean age ± SD = 36.3 ± 15.7; SMC: Mean age ± SD = 50.5 ± 9.4	preclinical period to dementia stage	seed-based correlation analysis	increased diffusivity of the left hippocampus-PCC circuit in presymptomatic mutation carriers; impaired caudate-rMFG and putamen rMFG circuits in APP gene mutation carriers; increased fiber numbers of putamen-rMFG circuit in PSEN1 gene mutation carriers.	2020
	Ewers M. et al. (Chhatwal et al., 2013)	*PSEN1*, *PSEN2*, *APP*	N (mutation carriers) = 108; N (mutation non-carriers) = 71	Mean age ± SD = 38.0 ± 10.5	preclinical period to dementia stage	seed-based correlation analysis	higher fMRI-assessed system segregation to be associated with an attenuated effect of estimated years from symptom onset on global cognition	2021

ADAD, autosomal dominant Alzheimer's disease; PSEN, presenilin; APP, amyloid precursor protein; CDR, clinical dementia rating; aMCI, amnestic mild cognitive impairment; AMC, asymptomatic mutation carrier; SMC, symptomatic mutation carrier; MTL, medial temporal lobe; rMFG, rostral middle frontal gyrus; DMN, default mode network; BOLD, blood oxygen level dependent.

The involvement of the precuneus/PCC is significant in the development of ADAD. Early amyloid deposition, abnormal structure, and reduced metabolism in these regions have been observed in ADAD (Johnson et al., 1998; Quiroz et al., 2018; Yokoi et al., 2018; Sanchez et al., 2021). Changes in the PCC and parietal cortex in task-related fMRI in asymptomatic subjects at risk for ADAD further suggest that the posterior cortical regions play key roles in the development of dementia.

The anterior cingulate gyrus and frontal lobes are also vulnerable regions in the functional imaging studies of ADAD. During the novelty encoding trials (Ringman et al., 2011), decreased BOLD signals in the anterior cingulate gyrus bilaterally and the left frontal pole were found in pre-symptomatic mutation carriers, compared with matching cognitively normal family members. In addition, decreased BOLD activity in regions of the left middle and inferior frontal gyri, the left frontal operculum, and the left lateral occipital cortex was also found in symptomatic mutation carriers during the visual memory encoding task (Sala-Llonch et al., 2013). The anterior cingulate correlates with the striatum *via* frontal-subcortical circuits (Ringman et al., 2011), and abnormal frontostriatal connectivity in both *APP* and *PSEN1* mutation carriers and its association with general cognitive function were also reported by Quan et al. using rs-fMRI. The anterior cingulate and frontal regions are involved in certain higher-level functions, such as attention allocation, decision-making, emotion, and memory. The anterior cingulate is also part of the salience network (Seeley et al., 2007), which might be selectively activated during the processing of novel stimuli. Decreased glucose metabolism and cerebral blood flow in the anterior cingulate in pre-symptomatic subjects carrying *PSEN1* mutations (Johnson et al., 2001), abnormalities in functional connectivity in aging, and mild cognitive impairment have been described (Cera et al., 2019).

A series of task-related fMRI studies were conducted in the big Colombian pedigree (*PSEN1* E280A) to explore brain activity in children (9–17 years old) (Quiroz et al., 2015), young adults (18–26 years old) (Reiman et al., 2012), and middle-aged adults (average age 33.7 years old) (Quiroz et al., 2010), who were all younger than 44 years old (mean age at onset of the disease (Acosta-Baena et al., 2011)). The encoding and viewing of novel face-name pairs (associative memory functioning task) were employed among these subjects. The analysis focused on the hippocampal system in the middle-aged adult group. Compared to non-carriers, cognitively intact *PSEN1* mutation-carrying adults demonstrated hyperactivation within the right anterior hippocampus during the encoding of novel associations. In young adults, mutation carriers showed significantly greater activation in the hippocampal and parahippocampal regions and less deactivation in the precuneus and posterior cingulate regions. Interactions remained significant in the right hippocampus, the right parahippocampal gyrus, the right precuneus, and the right posterior cingulate regions, after correction for multiple comparisons. Compared to non-carriers, mutation-carrying children appeared to have less deactivation in the posterior parietal regions. However, there were no significant differences between the groups in MTL activation, either when controlling for age or when looking at age-related slopes. In summary, compared to non-carriers, *PSEN1* E280A mutation carriers showed less deactivation in the precuneus and posterior cingulate regions during teenager and young adulthood, while the increased activity of the hippocampal and parahippocampal regions began from early adulthood and lasted until middle adulthood during memory association tasks.

In general, abnormalities in brain activity were found in the hippocampus, the MTL, the posterior cortex, the anterior and posterior cingulate cortices, and the middle and inferior frontal regions. These regions are also critical for cognitive function and show structural and pathological changes during the early phase of ADAD. The results of different studies vary in the affected brain regions and changes in activity. Possible explanations for these inconsistent results may be due to discrepant tasks, different populations, subjects' ages, and levels of cognition. Unified and standard task performance is needed in future studies when conducting meta-analyses.

RESTING-STATE NETWORKS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE

Resting-state functional magnetic resonance imaging, which evaluates brain regional interactions during the resting condition, can be used to study patterns of intrinsic brain connectivity or functional work *in vivo*. rs-fMRI measures spontaneous low-frequency fluctuations in the BOLD signal to investigate the functional architecture of the brain and allows the identification of various resting-state networks, or spatially distinct areas of the brain that demonstrate synchronous BOLD fluctuations at rest. Neural networks in rs-fMRI include several components (Moussa et al., 2012), with the default mode network (DMN) being the most studied and easily visualized network (Buckner, 2012). The DMN involves the precuneus and PCC, the parietal and temporal cortices bilaterally, the medial prefrontal cortex (mPFC), and some regions within the hippocampal memory system. Exploring the changes in restating state networks in ADAD may provide non-invasive functional imaging biomarkers for early diagnosis and interventions in ADAD.

In a DMN study of children, who were much younger than the estimated age of onset, in the big Colombian pedigree (Quiroz et al., 2015), no differences in functional connectivity in the whole network metric (six pre-defined nodes) were found. However, greater functional connectivity between the PCC and the bilateral MTL regions was found in mutation carriers than in non-carriers. No reduction in functional connectivity was observed in the mutation carriers. The opposite results were found in other studies using the independent component correlation algorithm (Chhatwal et al., 2013), in which functional connectivity within much of the DMN was decreased in ADAD mutation carriers compared with non-carriers. The most apparent decreased connectivity was with the major posterior node of the DMN (precuneus/posterior cingulate, PPC), along with the anterior node of the DMN (mPFC) and bilateral parietal cortices. Furthermore, compared with non-mutation carriers, functional connectivity in the PPC and right parietal cortex was decreased in asymptomatic mutation carriers, whereas decreased functional connectivity in the PPC, mPFC, and the left and

right parietal cortices was observed in symptomatic mutation carriers. More complex and divergent results were reported by Sala-Llonch et al. (2013). The anterior components of the DMN were increased in asymptomatic subjects and decreased in symptomatic subjects, while the posterior components of the DMN were decreased in asymptomatic subjects and increased in symptomatic subjects, compared with controls. However, these studies also found that decreased functional connectivity within both the posterior and anterior DMN in the pre-symptomatic stage of ADAD, and connectivity disruption within the posterior DMN was disrupted earlier (Zhao et al., 2020). Quan et al. (2020) provided novel evidence of changes in neural circuits in ADAD using rs-fMRI, combined with T1 structural MRI and diffusion tensor imaging. The anterior resting networks and frontostriatal circuits were affected in the asymptomatic stage of ADAD. More narrowly, frontostriatal circuits were impaired and functional connectivity was decreased in *APP* mutation carriers, while the connectivity of the putamen-rostral middle frontal gyrus (putamen-rMFG) showed increases in *PSEN1* mutation carriers. In summary, both anterior and posterior functional connectivity of the DMN can be affected in pre-symptomatic and symptomatic subjects, with the PCC, MTL regions, and pre-frontal cortex being more prominent. Meanwhile, altered functional connectivity in mutation carriers has been observed for several years or even over a decade before symptom onset (Sala-Llonch et al., 2013; Thomas et al., 2014). Furthermore, a significant interaction between mutation carrier status and estimated years from symptom onset (EYO) with a significant negative correlation between fMRI and EYO in mutation carriers was also demonstrated, but not in non-carriers. Interestingly, less fMRI deactivation of the parietal regions in the absence of MTL alterations was also observed, which suggests that functional abnormalities in the parietal region may precede MTL changes early in the disease. A hypothesis has been raised that higher segregation of the functional networks represents a functional mechanism underlying cognitive resilience in AD, and higher fMRI-assessed system segregation was found to be associated with an attenuated effect of EYO on global cognition (Ewers et al., 2021).

Differences in resting-state networks were compared between ADAD and aging, and between ADAD and LOAD. In general, the degradation pattern of functional connectivity in ADAD was similar to that in LOAD (Thomas et al., 2014), but it was different from that in aging (Chhatwal et al., 2018). Inter- and intra-network functional connectivity decreases with increasing Clinical Dementia Rating (CDR) were similar for both ADAD and LOAD in multiple resting-state networks, including DMN. With some subtle differences observed, there was a modestly greater effect on disease severity seen in ADAD than in LOAD, which possibly reflected a faster spread of pathology across diseased connections in ADAD. As for ADAD versus aging, cognitive networks were preferentially degraded in ADAD, with changes in motor and visual networks seen only in the advanced stages. A contrasting degradation pattern was observed in aging subjects, where visual networks degraded to a similar or greater degree than cognitive networks. Both studies also demonstrated that inter-network connections were preferentially targeted in ADAD, with intra-network connections relatively spared. The results suggest that particular networks are selectively vulnerable in ADAD and support the 'network diffusion' models of AD progression (Raj et al., 2015), which preferentially degrades connections within cognitive networks. This evidence supports that aging and AD demonstrate distinct pathophysiological mechanisms and that ADAD may serve as an effective model to study LOAD pathophysiology.

CONCLUSION AND PERSPECTIVES

The hippocampus, the medial temporal region, the precuneus, the inferior parietal cortex, and the anterior and posterior cingulate cortices are key hubs in both task-related and rs-fMRI in ADAD. Inter- and intra-networks in these regions, along with the striatum, present abnormal functional connectivity in the early pre-symptomatic stages of ADAD, with the former being much more prominent. The regional brain activity and functional connectivity decrease as subjects carrying mutations approach the estimated age of onset or cognitive function gradually deteriorates.

As for neural reserves, most previous studies have been conducted in aging and SAD populations, while similar studies in ADAD are scarce. A recent study demonstrated that higher levels of global functional connectivity of the left frontal cortex were associated with attenuating effects of AD pathology on cognition in prodromal ADAD (mild cognitive impairment due to AD plus very mild AD dementia) (Franzmeier et al., 2018). It has been demonstrated that increased connectivity of frontal hubs is associated with cognitive training (Takeuchi et al., 2017), transcranial magnetic stimulation, transcranial direct-current stimulation (Chen et al., 2013; Kim et al., 2016), or physical exercise (Duzel et al., 2016), and increased hub connectivity is associated with better cognition (Cole et al., 2012; Liu et al., 2017). ADAD provides a good vehicle for conducting early and longitudinal neuroimaging studies or intervention studies to further elucidate how neural reserve and compensation evolve at different stages of ADAD and the relationship between cognitive reserve and its neural correlates. Exploring the mechanism under the neural network-level treatment helps to discover the potential molecular targets of ADAD, which helps in the development of drug therapy.

Considering that ADAD accounts for less than 1% of all AD cases, fMRI studies on ADAD are insufficient and the results are inconsistent. These findings are difficult to integrate due to different choices of subjects, tasks, regions of interest, etc. Moreover, cross-center effects are not yet widely recognized. ADAD is a subtype of rapidly progressive dementia with certain heterogeneity, and its fMRI characteristics require more detailed hierarchical analysis based on age, genotype, biomarkers, etc. is warranted. Future fMRI studies in ADAD are needed to optimize more specific connectivity composites, investigate the network-level neural underpinnings of cognitive alterations, and clarify the chronological order of fMRI changes and other pathophysiological biomarkers of ADAD progression. Using multi-network or inter-network composite connectivity measures may be particularly useful for increasing the specificity of functional connectivity MRI

biomarkers and reducing the impact of common confounding conditions. Moreover, technical factors are critical in assessing fMRI: small amounts of head movement that are not easily detected and multiple different methods of data analysis can confound the results. Subsequent studies can compare different techniques to obtain sensitive and stable parameters and combinations of parameters and sites for detecting microstructural changes. Reliable multi-center studies will bring major progress in fMRI research on ADAD.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

FUNDING

This study was supported by the Key Project of the National Natural Science Foundation of China (81530036); the National Key Scientific Instrument and Equipment Development Project (31627803); the Mission Program of Beijing Municipal Administration of Hospitals (SML20150801); the Beijing Scholars Program; the Beijing Brain Initiative from Beijing Municipal Science and Technology Commission (Z161100000216137); the Innovation Base Training and Development Special Program (Z171100002217007); the CHINA-CANADA Joint Initiative on Alzheimer's Disease and Related Disorders (81261120571), and the Project for Outstanding Doctor with Combined Ability of Western and Chinese Medicine.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 05 August 2022
DOI 10.3389/fnagi.2022.938789

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 08 May 2022
ACCEPTED 11 July 2022
PUBLISHED 05 August 2022

CITATION
Long J, Song X, Wang Y, Wang C, Huang R and Zhang R (2022) Distinct neural activation patterns of age in subcomponents of inhibitory control: A fMRI meta-analysis. *Front. Aging Neurosci.* 14:938789. doi: 10.3389/fnagi.2022.938789

Distinct neural activation patterns of age in subcomponents of inhibitory control: A fMRI meta-analysis

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Inhibitory control (IC) is a fundamental cognitive function showing age-related change across the healthy lifespan. Since different cognitive resources are needed in the two subcomponents of IC (cognitive inhibition and response inhibition), regions of the brain are differentially activated. In this study, we aimed to determine whether there is a distinct age-related activation pattern in these two subcomponents. A total of 278 fMRI articles were included in the current analysis. Multilevel kernel density analysis was used to provide data on brain activation under each subcomponent of IC. Contrast analyses were conducted to capture the distinct activated brain regions for the two subcomponents, whereas meta-regression analyses were performed to identify brain regions with distinct age-related activation patterns in the two subcomponents of IC. The results showed that the right inferior frontal gyrus and the bilateral insula were activated during the two IC subcomponents. Contrast analyses revealed stronger activation in the superior parietal lobule during cognitive inhibition, whereas stronger activation during response inhibition was observed primarily in the right inferior frontal gyrus, bilateral insula, and angular gyrus. Furthermore, regression analyses showed that activation of the left anterior cingulate cortex, left inferior frontal gyrus, bilateral insula, and left superior parietal lobule increased and decreased with age during cognitive inhibition and response inhibition, respectively. The results showed distinct activation patterns of aging for the two subcomponents of IC, which may be related to the differential cognitive resources recruited. These findings may help to enhance knowledge of age-related changes in the activation patterns of IC.

KEYWORDS

inhibitory control, response inhibition, cognitive inhibition, fMRI, aging

Introduction

Inhibitory control refers to the ability to suppress unwanted actions that are not appropriate for the current situation or to resist distractions and adapt to conflicting situations (Goldman-Rakic, 1996; Aron, 2007; Aïte et al., 2018). By doing so, humans can selectively attend to task-relevant information and engage in goal-directed rather than habitual actions, as well as staying away from dangerous environments. Dysfunctional inhibitory control is considered to be one of the symptoms of various disorders, including affective and anxiety disorders (Paus et al., 2008), eating disorders (Bartholdy et al., 2019), learning difficulties (Eickhoff et al., 2008), and substance abuse (Steele et al., 2018). More importantly, it is thought to be an essential cause of cognitive function decline in the aging brain (Zacks et al., 2000). Better understanding of the developmental trajectory of inhibitory control and its neural correlates across the healthy lifespan could not only help to identify the pivotal time point at which inhibitory control and related neural networks decline over the lifespan but will also help to formulate an early intervention strategy for people who are at risk of inhibitory control deficits.

Behavioral and neural developmental trajectory of inhibitory control

In the recent years, there has been an increase in the number of studies examining the behavioral and neural developmental trajectory of inhibitory control across the lifespan (refer to **Supplementary Figure 1**). However, there is a lack of agreement in the results of existing studies examining the behavioral developmental trajectory of inhibitory control. For example, some studies have suggested a steady increase in inhibitory control from adolescence to adulthood (Velanova et al., 2008; Aïte et al., 2018), and some studies revealed a lack of improvement in inhibitory control from adolescence to adulthood (Luna et al., 2004; Ordaz et al., 2013; Humphrey and Dumontheil, 2016), while other studies have found that inhibitory control develops until adolescence and then declines slightly from young adulthood to old age (Schachar and Logan, 1990; Williams et al., 1999).

In neuroimaging research examining the neural developmental trajectory of inhibitory control, the results are also not consistent. Increased frontal activation in adults compared with children has been observed in some fMRI studies (Bunge et al., 2002; Tamm et al., 2002; Luna et al., 2004). Rubia et al. (2013) reported that superior performance in adults was paralleled by increased activation in a network comprising prefrontal and parietal cortical regions in cognitive inhibition. Moreover, Vink et al. (2014) showed increased activation with age during response inhibition in the right inferior frontal cortex and supplementary motor area. Using a Go/NoGo task, Cope et al. (2020) reported a significant positive linear activation associated with age in the frontal, temporal, parietal, and occipital cortices, which means that activation in these regions during response inhibition increased with age. However, other neuroimaging studies have reported stronger activation during cognitive inhibition in the frontal and parietal lobes in children and adolescents aged 9–12 years compared with adults aged 20–30 years (Booth et al., 2003). Durston et al. (2002) reported stronger activation in the bilateral ventral prefrontal cortex, right parietal lobe, and right dorsolateral prefrontal cortex for children than adults during a response inhibition task.

Previous meta-analyses have also compared brain activation across different age groups to explore the age effect of brain activation during the process of inhibitory control (Nielson et al., 2004; Fernandez-Ruiz et al., 2018). For example, Nielson et al. (2004) reported that activation during inhibition occurred predominantly in the right prefrontal and parietal regions in participants older than the young adult group; in their study, the researchers compared data collected from four different age groups (18–31 years for young adults, 33–55 years for middle-aged adults, 62–72 years for young elderly, and 73–78 years for elderly). Moreover, Fernandez-Ruiz et al. (2018), in a study including individuals aged 18–25 years for young adults and 49–83 years for older adults, reported decreased activation in the anterior cingulate and increased activation in the dorsolateral prefrontal cortex in the older group but not in the younger group. The above studies, which had a lack of agreement on the developmental patterns of behavioral performance and neural activation during inhibitory control, suggest that the developmental patterns of inhibitory control with aging need to be further clarified.

The lack of agreement in the existing studies on the behavioral and neural developmental trajectory of inhibitory control across the lifespan may be due to studies including samples with limited age ranges or the fact that few existing studies or theories have systematically differentiated age-related changes in different inhibitory control tasks. For example, Aïte et al. (2018) recruited 160 participants aged 10–23 years to investigate the developmental patterns of inhibitory control and the degree of specificity of inhibitory control in children, adolescents, and adults (not including older adults), whereas Velanova et al. (2009) only recruited 98 individuals aged 8–27 years in their study. Similarly, Humphrey and Dumontheil (2016) only included 90 participants aged 12–18 years in their study, which revealed a lack of improvement in inhibitory control from adolescence to adulthood, and did not include younger children or older adults as participants. Furthermore, Ordaz et al. (2013) carried out a longitudinal study including a total of 123 individuals spanning the age range of 9–26 years.

Most current studies on the behavioral and neural developmental trajectory of inhibitory control across the lifespan include only a single type of inhibitory control task

(Booth et al., 2003; Andrés et al., 2008; Anguera and Gazzaley, 2012). For example, Anguera and Gazzaley (2012) reported that in a stop signal task, the stop signal reaction time of older adults was slower than that observed in younger adults, suggesting an age-related deficit in inhibitory control in the older population, whereas Booth et al. (2003) reported that children had more errors and slower reaction times compared to adults in a selective attention task. Similarly, Andrés et al. (2008) found that aging affected the ability to cancel a strong response in a stop signal task but did not affect performance in a Stroop task. Notably, Hasher and Zacks (1988) suggested that working memory capacity, as a core component of executive function, was constrained by the resources demanded in different working memory tasks and declined across the adult lifespan. The above studies suggest that since inhibitory control is also a subcomponent of executive function (Miyake et al., 2000), and different developmental trajectories of inhibitory control across the lifespan may also be impacted by varying degrees of task demand (Sebastian et al., 2013a). Therefore, there is a critical need to clarify the similarities and differences between different inhibitory control tasks (Dalley et al., 2011; Swick et al., 2011; Sebastian et al., 2013b) and further explore the developmental trajectory of inhibitory control through a wider age range under the framework of different subcomponents of inhibitory control.

Subcomponents of inhibitory control and its neural correlates

In the recent times, an increasing number of studies have not only focused on explaining the diversity, scope, and range of inhibitory control functions, but have explored the intrinsic variability of different components of inhibitory control. These studies have suggested that inhibitory control is not a unitary construct, but is the one which can be further differentiated into different subcomponents (Aron, 2011; Brevers et al., 2017; Gavazzi et al., 2021). For example, by capturing the temporal dynamics in the processes of inhibitory control, Braver (2012) described a dual mechanism of control (DMC) framework, which hypothesized that inhibitory control operates through two distinct modes—proactive control and reactive control—depending on the time that the action was withheld. Proactive inhibition is considered as a "top-down" model of inhibitory control, which actively maintains goal-relevant information and facilitates the suppression of the coming action before the occurrence of cognitive events (Braver, 2012). In contrast, reactive inhibition is a "bottom-up" form of control and is thought to be a stopping mechanism triggered by an already-initiated motor response (Aron, 2011; Meyer and Bucci, 2016). Experimental evidence from neuroimaging studies shows partially overlapping regions such as the frontoparietal circuit activated in the processes of both reactive and proactive inhibitions, which may reflect cognitive function or brain network sharing between these two inhibitory control processes (Zandbelt et al., 2011; van Belle et al., 2014). These studies suggest that dual mechanisms of control, namely, proactive inhibition and reactive inhibition, may not be sensitive to the distinct cognitive function developmental trajectory.

To differentiate the cognitive process during inhibitory control, inhibitory control can also be classified into two subcomponents—cognitive and response inhibitions—depending on the cognitive process of different inhibition targets in inhibitory control tasks (Hung et al., 2018). Cognitive inhibition involves the suppression of competing cognitive processing to solve relevant problems, whereas response inhibition involves the suppression of a prepotent response or an already-initiated action to perform a different, more context-appropriate response (Sebastian et al., 2013a; Kan et al., 2021). The dissociation of cognitive inhibition and response inhibition may provide useful information to further understand different manifestations of inhibitory dysfunction, which will greatly benefit clinical research.

Differences between inhibition difficulties and complexity of the two types of inhibition tasks might originate from the differences in cognitive resources recruited in these subcomponents of inhibitory control tasks (Sebastian et al., 2013a). Stahl et al. (2014) used a multicomponent modeling approach and showed that the control of response-related interference is not a unitary construct and that cognitive interference can be separated from response inhibition. Noreen and MacLeod (2015) showed no significant correlations or commonalities between different inhibition tasks such as Stroop, Go/NoGo, and stop signal tasks, suggesting that different inhibitory control tasks primarily assess different aspects of inhibition processes and involve different brain system or neural mechanisms. This may be attributed to the variety of inhibitory control tasks with different demands of cognitive resources, the latter of which may eventually result in the differences in inhibition behavioral performance with increasing age across the healthy lifespan.

Cognitive inhibition can be captured by paradigms including the Stroop, Flanker, and Simon and stimulus response compatibility (SRC) (Stahl et al., 2014; van Velzen et al., 2014; Almdahl et al., 2021). In the Stroop or Flanker tasks, participants are required to suppress interference due to stimulus competition or irrelevant information and need to resolve a conflicting representation arising from the cognitive level (Hung et al., 2018). A measure of cognitive inhibition is thus the difference in reaction time in incompatible compared to compatible or baseline trials (Sebastian et al., 2013a). Moreover, response inhibition is usually assessed by tasks such as the antisaccade task, Go/NoGo task, or stop signal task. A measure of response inhibition is the proportion of correctly withheld responses compared to incorrectly withheld actions in a NoGo or antisaccade stimulus, or reaction time in a stop signal task, which may reflect the latency of the inhibition process.

In line with the findings of behavioral studies regarding cognitive inhibition and response inhibition, studies characterizing the neural correlates of inhibitory control have also found a significant difference in neural correlates between the two components. For example, Rubia et al. (2006) demonstrated a stronger activation of the cingulo-opercular network in cognitive inhibition compared to response inhibition, whereas Sebastian et al. (2013a) revealed that cognitive inhibition activated the pre-SMA and parietal regions to a greater extent than response inhibition. More recently, through quantitatively synthesizing the published studies on inhibitory control, Hung et al. (2018) reported stronger activation of the dorsal frontal and parietal lobe in cognitive inhibition tasks compared to stronger activation of the frontostriatal network including the dorsal anterior cingulate cortex, supplementary motor cortex, lateral prefrontal cortex, basal ganglia, and parietal regions in response inhibition tasks, whereas the left anterior insula was found to be consistently activated in cognitive inhibition and response inhibition. In sum, the findings of distinct inhibitory networks in different subcomponents of inhibitory control provide supporting evidence for the differences in neural correlates between cognitive inhibition and response inhibition. Furthermore, Sebastian et al. (2013a) reported that with an increasing demand of inhibition tasks, further additional brain regions including the frontal and parietal cortices were recruited in older adults. This finding may confirm that age-related distinct brain region activation patterns in the two subcomponents of inhibitory control across the lifespan may originate from the different cognitive demand involved in the two subcomponents of inhibitory control processes; thus, this may reflect the behavioral developmental trajectory of inhibitory control.

In this study, we investigated how neural activation during the two subcomponents of inhibitory control changes across the healthy lifespan with aging using meta-analytic technology. The study had two aims: that first was to characterize the common or distinct neural correlates in the two subcomponents of inhibitory control and the second was to identify the distinct age-related activation pattern in the two subcomponents of inhibitory control. Since the cognitive resources recruited in

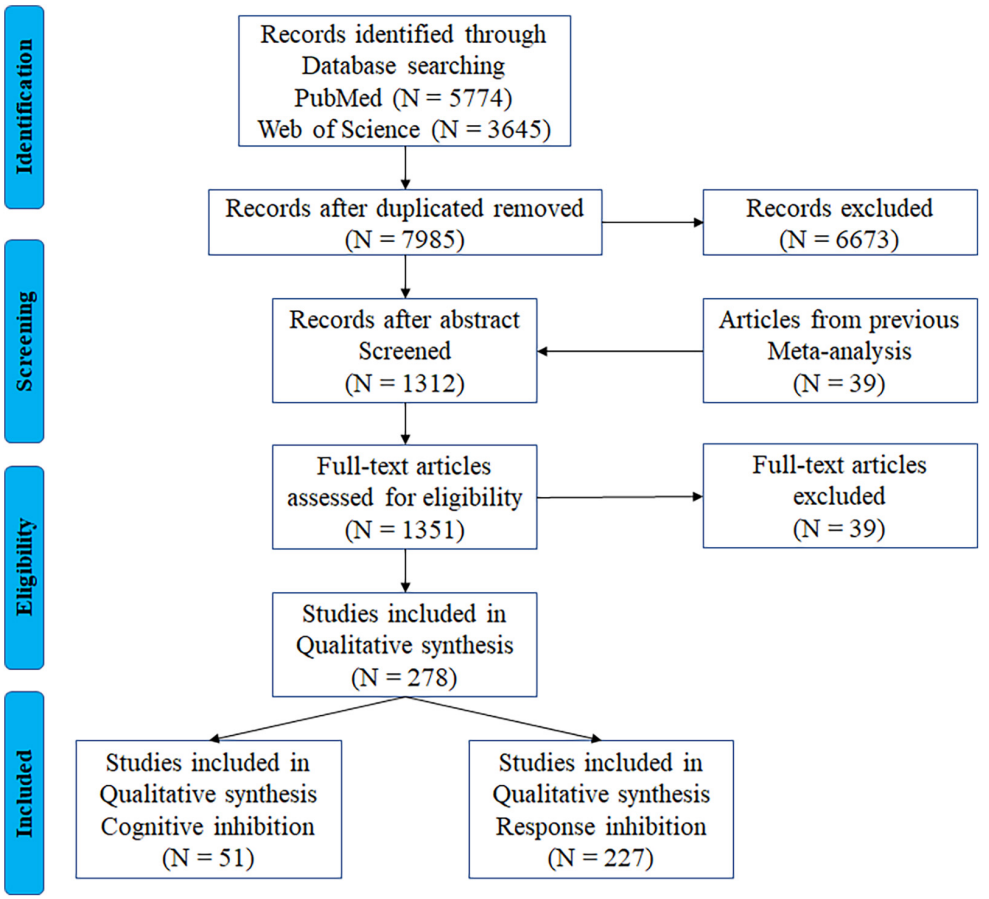

FIGURE 1
PRISMA flowchart for the identification and eligibility of articles. *N* = number of articles.

the two subcomponents are different, we hypothesized that the activation patterns of inhibitory control may show distinct age-related trajectories in the two subcomponents of inhibitory control, or differential activation patterns may be shown across different age groups in cognitive and response inhibitions.

Methods

Literature search and article selection

First, two online citation indexing services—PubMed and Web of Science—were searched. This search used the keywords "fMRI" with "interference resolution," "action withholding," "action cancellation," "response inhibition," "cognitive inhibition," "inhibitory control," "stop signal," "stopping," "go nogo," "action restraint," or "countermanding," including articles published prior to April 2020, yielding a total of 9,419 articles. After removing duplicates, a total of 7,985 articles were screened. We then compiled 39 eligible articles identified in a previous meta-analysis (Zhang R. et al., 2017). The following exclusion criteria were applied to eliminate articles that were not directly relevant to this study: (1) non-original studies (e.g., review, abstract), (2) studies that did not report results either in Talairach or Montreal Neurology Institute (MNI) coordinate space, (3) studies with a sample size below five, (4) studies on older adults with dementia, head injury, stroke, or any neurological or other psychiatric disease, (5) pharmacological or training-related studies, unless they conducted a baseline comparison and fulfilled our inclusion criteria, (6) studies with no control group or within-group contrast, (7) studies that used positive or negative stimulation only in inhibition tasks. A total of 278 articles were included in the current meta-analysis. **Figure 1** shows the detailed search and selection procedures. The final dataset was then divided into the two subcomponents of inhibitory control: 51 articles on cognitive inhibition and 227 articles on response inhibition.

Data extraction

We extracted the following information from each study: authors, year of publication, sample size, experimental design, paradigms, mean age with the age range, task contrasts, stimulation types, and cluster coordinates in the MNI or Talairach space.

Experiment categorization

Cognitive inhibition

Cognitive inhibition is the inhibitory process of suppression of competing cognitive processing to solve relevant problems (Hung et al., 2018). For the cognitive inhibition domain, we included commonly used cognitive interference paradigms (Hung et al., 2018): Stroop, Flanker, Simon task, and SRC. We examined the changes in activation between incongruent and neutral or incongruent and congruent conditions to measure straightforward processing of cognitive interference. A total of 51 articles consisting of 54 experiments were included to explore the neural correlates of cognitive inhibition. The characteristics of each study are listed in **Supplementary Table 1**.

Response inhibition

Response inhibition is the process of suppression of a prepotent response to perform a different, more context-appropriate response (Hung et al., 2018). To measure the response inhibition, we included the classical paradigms, including antisaccade, Go/NoGo, and stop signal tasks, which primarily require the inhibition of prepotent motor responses. Qualified response inhibition experimental contrasts measured the differences in activation between go and no-go or stop conditions. A total of 227 articles comprising 236 contrasts using the antisaccade, Go/NoGo paradigm, or stop signal paradigm were employed to identify the response inhibition-related activation patterns.

Multilevel kernel density analysis

Meta-analyses were performed using the Multilevel kernel density analysis (MKDA) (Wager et al., 2007) toolbox[1] to identify the brain regions activated during inhibitory control. Peak effect coordinates from each study were convolved with a spherical kernel (r = 16 mm) (Wager et al., 2004) to generate comparison indicator maps (CIMs), with a value of 1 indicating that "this study activated near this voxel" and a value of 0 indicating that "this study did not activate near this voxel." The CIMs were averaged to yield the proportion of studies in which the activation was observed within 16 mm of each voxel. The family-wise error (FWE) rate was estimated to correct for multiple comparisons (5,000 permutations).

Previously used meta-analyses, such as the activation likelihood estimate (ALE), count how many peak coordinates are within each voxel divided by the brain regions and compare this to the number expected by chance if the peak coordinates were randomly distributed in the brain. This method is limited by the consequence that the peak coordinates in any single study may overly influence the results from analyses (Radua and Mataix-Cols, 2012). Using MKDA may overcome this limitation by separating the peaks of each study. In the MKDA method, the null hypothesis is that the n peak coordinates reported in the set of studies to be analyzed are randomly and uniformly distributed throughout the gray matter. Thus, in this study,

1 https://www.colorado.edu/ics/research/wager-lab

the meta-analytic results represent common activated regions across studies: regions in which the significant activation was observed in the local neighborhood by more studies than would be expected by chance ($p < 0.05$, FWE-corrected across the entire brain). Specifically, to characterize brain activation patterns, first, we identified brain regions that showed significant convergence across 278 studies comprising 4,393 foci from 290 contrasts. Then, contrast analyses were conducted to verify the differences in cognitive demand for the two subcomponents of inhibitory control and capture the selectively or preferentially activated brain regions for two subcomponents of inhibitory control: cognitive inhibition vs. response inhibition. All cluster coordinates were analyzed in Montreal Neurological Institute (MNI) standard stereotaxic spaces.

Effects of age on subcomponents of inhibitory control

Meta-regression analyses with age

To further assess age-related change in activation patterns in the subcomponents of inhibitory control, the effect-size seed-based d mapping (ES-SDM) toolbox (SdmPsiGui-v6.21 from the Seed-based d Mapping project) was used to perform meta-regression analyses because the ES-SDM software can provide accurate results of regression analyses incorporating meta-regression methods. This is achieved by first using peak coordinates and their statistical values to recreate statistical parametric maps and then conducting an image-based meta-analysis (Radua and Mataix-Cols, 2012). The full width at half maximum (FWHM) in SDM was set at 20 mm (Radua and Mataix-Cols, 2012) by default to control for false positives and the resulting statistical maps were thresholded at $p < 0.05$ to control for family-wise error rate. We performed two meta-regression analyses in ES-SDM. Data involved in the meta-regression analyses were derived from response inhibition contrasts and cognitive inhibition contrasts separately. Given that different age ranges were reported in the original articles, the age computed in the meta-regression analysis as a continuous variable was determined by the mean age of each sample in the original articles. The results from the two regression analyses were then compared to identify brain regions with distinct age-related activation patterns in the two subcomponents of inhibitory control.

Meta-analyses across different age groups

Further, given that age was computed in the meta-regression analysis as a continuous variable determined by the mean age of each sample in the original articles, the mean age was affected by extreme values, which cannot well represent the age distribution of all subjects in each original study. As mentioned above, to more completely explore the age-related changes in the two subcomponents of inhibitory control within individuals of different ages, we performed additional MKDA analyses as validation analyses. We divided the datasets from all articles included in the current meta-analysis into four age groups: under 18 years for under-aged children, 18–35 years for young adults, 35–55 years for middle-aged adults, and 55–80 years of age for older adults. Then, we performed contrast analyses and computed the differences among all age groups in the two subcomponents of inhibitory control: under-aged children vs. young adults, young adults vs. middle-aged adults, middle-aged adults vs. older adults, under-aged children vs. middle-aged adults, young adults vs. older adults, and under-aged children vs. older adults.

Validation analyses

Additional validation analyses were performed to reduce the impact of the number of experiments, the different types of inhibition tasks, and the behavioral performance reported in the studies included in the results of the current meta-analysis.

First, studies on response inhibition (236 experiments of Go/NoGo and stop signal tasks) included a much larger number of experiments compared to those on cognitive inhibition (54 experiments). To test the effect of the number of experiments, we randomly selected 54 contrasts from the response inhibition data and repeated the MKDA and meta-regression analysis with age as a variable using the same settings.

Second, leave-one-out analysis was performed to test homogeneity in the cognitive inhibition tasks and response inhibition tasks separately. For the two subcomponents of inhibitory control, we removed each type of inhibition task one at a time: including Flanker, Simon, Stroop, WCST, and other tasks for cognitive inhibition, and tasks including antisaccade, Go/NoGo, and stop signal tasks for response inhibition. MKDA analyses were separately performed on the remaining studies with a total of five activation maps for cognitive inhibition and three activation maps for response inhibition. Then, we pooled the activation maps to obtain the overlapping rate maps for cognitive and response inhibitions, respectively. The overlap rate maps obtained from leave-one-out analysis and the results from MKDA on cognitive or response inhibition were then contrasted to test whether different tasks employed in studies influenced the activation patterns in the subcomponents of inhibitory control. Furthermore, since the meta-analysis results of cognitive inhibition and response inhibition identified different major regions (i.e., insula, inferior frontal gyrus, and angular gyrus), we conducted contrast analyses on the regions identified in the leave-one-out meta-analysis results for cognitive inhibition and response inhibitions separately.

Third, to investigate whether older adults that performed a task similarly to younger adults may show different patterns of activity to older adults who underperformed relative to younger

adults, we selected a total of 81 studies which reported task performance with successful inhibition in response inhibition tasks. Then, we performed a meta-regression analysis and several contrast analyses separately.

Results

Meta-analysis of all included inhibitory control experiments

The MKDA of the 278 studies showed significant activation of clusters in both hemispheres, including the frontal cortex, the angular gyrus, and the supplementary motor area (Figure 2A). The results are provided in Supplementary Table 2.

Brain activation patterns of each component

Brain activation patterns of cognitive inhibition

In both hemispheres, activated areas during the cognitive inhibition tasks included the inferior frontal gyrus, precentral gyrus, anterior insula, inferior parietal lobule, supplementary motor cortex, superior parietal lobule, superior frontal gyrus, middle cingulate gyrus, inferior frontal gyrus, and angular gyrus (Figure 2B and Table 1). Unilateral activations were observed in the right middle frontal gyrus.

Brain activation patterns of response inhibition

Data from response inhibition experiments revealed activations in the right middle frontal gyrus, the right angular gyrus that extended to the middle temporal gyrus and superior temporal gyrus, the right inferior temporal gyrus, and the left middle cingulate gyrus. In addition, activation areas in both hemispheres were observed in the supplementary motor cortex, middle cingulate gyrus, superior frontal gyrus, precentral gyrus, inferior frontal gyrus, anterior insula, inferior parietal lobule, and supramarginal gyrus (Figure 2C and Table 1).

Common and distinct activation patterns in the two subcomponents

Activation patterns common to the two subcomponents of inhibitory control were derived by conjunction analysis (Figure 3A). Regions commonly activated in the two subcomponents of inhibitory control included the following: (1) the supplementary motor cortex, which extended to the middle cingulate cortex and the superior parietal lobule in both hemispheres; (2) the inferior frontal gyrus, which extended to the middle frontal gyrus and insula in both hemispheres;

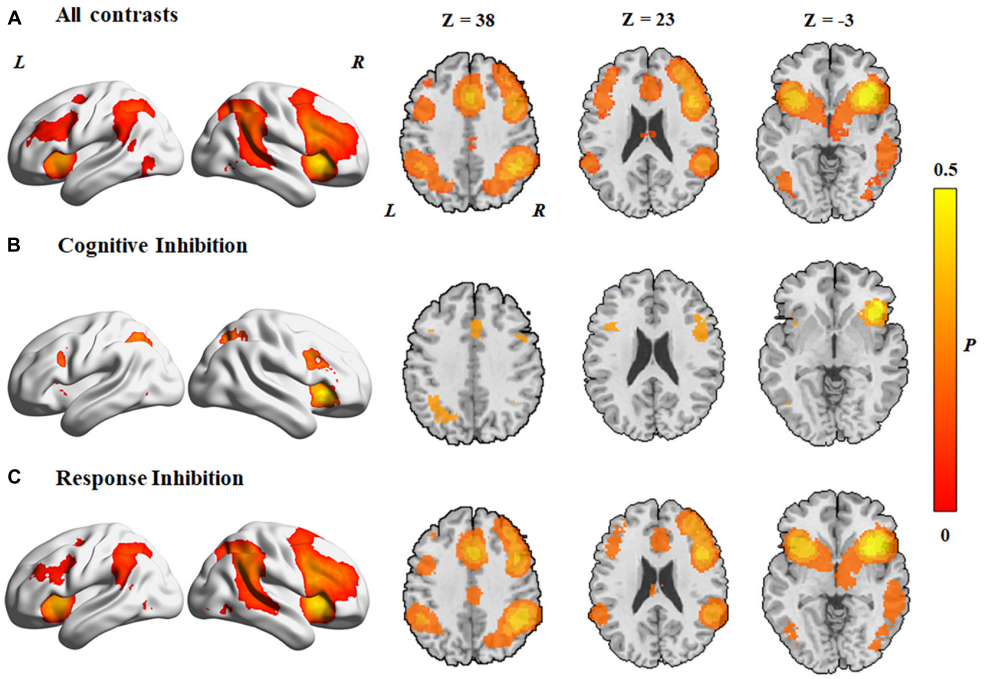

FIGURE 2
Concordance of brain activation from the MKDA analyses. **(A)** Brain areas activated by all contrasts. Brain areas activated in **(B)** cognitive inhibition and **(C)** response inhibition. The color bar represents the proportion of studies exhibiting the effect at the peak density weighted by sample size (P).

TABLE 1 Brain activation in two subcomponents of inhibitory control.

Regions	R/L	MNI			No.Voxs	Maximum P
		x	y	z		
Cognitive inhibition						
Angular Gyrus	R	26	−64	48	247	0.35
Inferior Frontal Gyrus	R	44	12	24	769	0.49
Inferior Frontal Gyrus	L	−40	14	20	281	0.37
Inferior Parietal Lobule	L	−30	−58	44	870	0.4
Inferior Parietal Lobule	R	34	−52	48	131	0.34
Insula	R	38	22	−2	1696	0.57
Supplementary Motor Area	L	−2	14	48	865	0.4
Response inhibition						
Angular Gyrus	R	30	−60	46	1627	0.38
Inferior Frontal Gyrus	L	−38	30	4	724	0.39
Inferior Frontal Gyrus	L	−42	18	22	1239	0.4
Inferior Frontal Gyrus	R	46	14	30	2630	0.45
Inferior Parietal Lobule	R	48	−44	40	2505	0.44
Inferior Parietal Lobule	L	−50	−44	42	1540	0.31
Inferior Parietal Lobule	L	−30	−58	48	1096	0.31
Inferior Temporal Gyrus	R	42	−70	−6	362	0.21
Insula	R	40	20	−2	4106	0.53
Middle Cingulate Cortex	R	4	30	34	1550	0.38
Middle Cingulate Cortex	R	2	−24	34	348	0.21
Middle Frontal Gyrus	R	36	42	24	2229	0.37
Middle Temporal Gyrus	R	56	−28	−2	653	0.27
Occipital Gyrus	L	−38	−66	−8	396	0.2
Pallidum	R	18	4	4	1664	0.42
Precentral Gyrus	R	34	2	50	1573	0.35
Precentral Gyrus	L	−34	−2	48	906	0.23
Precuneus	R	14	−68	44	357	0.27
Superior Temporal Gyrus	L	−8	2	6	1837	0.32
Superior Temporal Gyrus	R	56	−42	14	2109	0.38
Superior Temporal Gyrus	L	−58	−46	22	576	0.25
Supplementary Motor Area	R	4	10	52	4191	0.45
Thalamus	R	4	−18	14	336	0.22

Maximum P is the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size. The coordinates are Montreal Neurological Institute (MNI) standard stereotaxic spaces. The voxel size is 2 mm × 2 mm × 2 mm. R/L, right/left hemisphere.

(3) the right superior occipital gyrus and left middle occipital gyrus; and (4) the inferior parietal lobule and angular gyrus in both hemispheres.

Contrast analyses of cognitive inhibition and response inhibition revealed that significantly different regions were activated in the two subcomponents of inhibitory control. Specifically, compared to response inhibition, a higher level of activation was found during cognitive inhibition in the left superior parietal lobule (Figure 3B and Table 2). On the other hand, a higher level of activation during response inhibition compared to cognitive inhibition occurred in the frontal cortex including the bilateral insula and inferior frontal gyrus, the right middle frontal gyrus, and the right superior frontal gyrus, which extended to the bilateral putamen (Figure 3C and Table 2). Regions in the right middle temporal gyrus and right angular gyrus also showed a higher level of activation during response inhibition than in cognitive inhibition.

Age-related brain activation patterns of each component

Age-related change in the activation patterns in cognitive inhibition

In the cognitive inhibition tasks, results from the meta-regression analysis with age as a continuous variable across all studies showed a positive association with clusters in the followings: (1) the middle cingulate cortex, anterior cingulate cortex, and insula in both hemispheres; (2) the

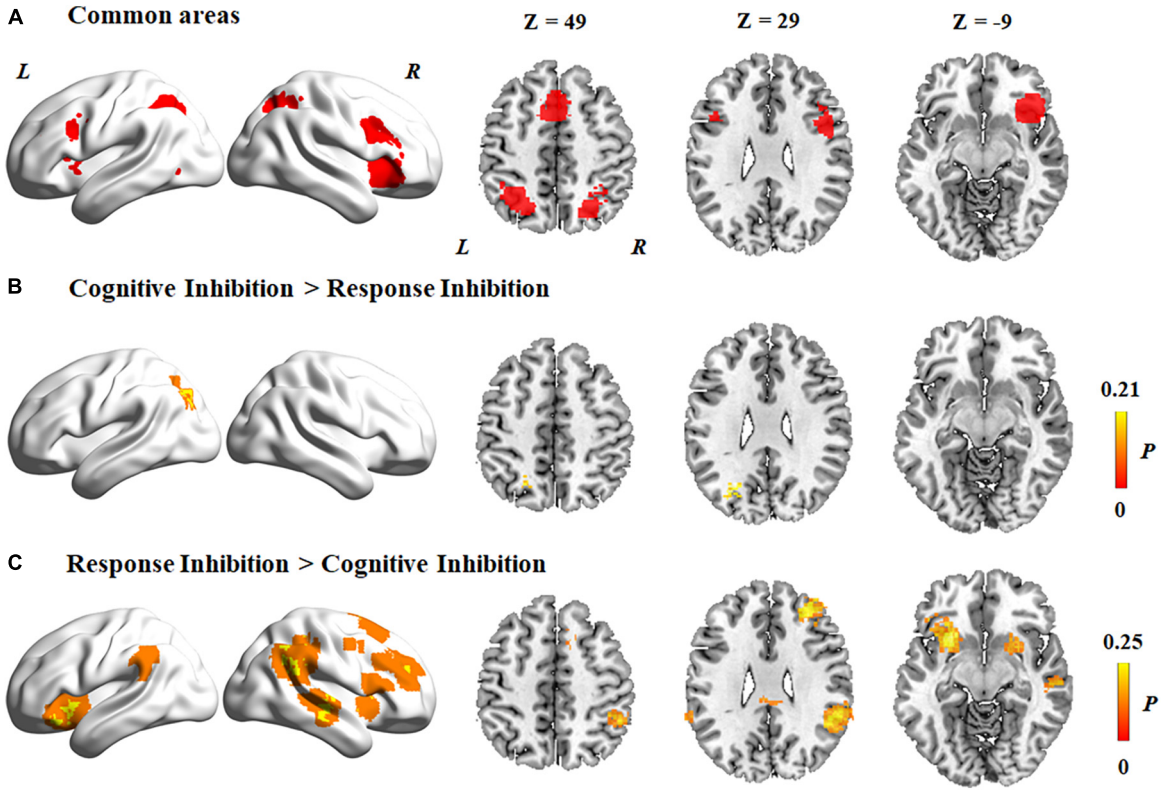

FIGURE 3
Common and distinct activation regions between two subcomponents. **(A)** Common areas between cognitive inhibition and response inhibition. **(B)** Higher activation in cognitive inhibition than response inhibition. **(C)** Higher activation in response inhibition than cognitive inhibition. The color bar represents the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size (P).

angular gyrus, superior parietal lobule, inferior frontal gyrus, and supplementary motor cortex in the left hemisphere. In addition, a negative association between age and clusters was found in the bilateral middle frontal gyrus, left inferior parietal lobule, right angular gyrus, and right inferior frontal gyrus (Figure 4A).

Age-related change in the activation patterns in response inhibition

Activation in the response inhibition tasks showed significant positive correlations with age in the right angular gyrus, right middle frontal gyrus, bilateral inferior parietal lobule, and bilateral middle cingulate cortex, whereas a negative correlation with age was found in the followings: (1) the anterior cingulate cortex, inferior frontal gyrus, insula, hippocampus, and superior parietal lobule in the left hemisphere and (2) the superior frontal gyrus, cerebellum, insula, and inferior frontal gyrus in the right hemisphere (Figure 4B).

Distinct activation patterns with age in subcomponents of inhibitory control

To characterize distinct brain regions with age-related changes in activation patterns in the two subcomponents of inhibitory control, we overlapped the results from regression analyses in the two subcomponents with age and found different age-related activation patterns in the subcomponents (Figure 4). Activation of inhibitory regions including the left anterior cingulate cortex, left inferior frontal gyrus, bilateral insula, and left superior parietal lobule showed a positive correlation with age in the cognitive inhibition tasks, but a negative association with age in the response inhibition tasks.

Brain activation patterns across different age groups for each component

Brain activation patterns across different age groups for cognitive inhibition

Contrast analyses among different age groups for cognitive inhibition showed that regions with significantly higher levels of activation in adults (including young, middle-aged, and older adults) than under-aged children were located in the bilateral inferior frontal gyrus, right insula, and left supplementary motor area (Figure 5A). Compared to young adults, the right insula

TABLE 2 Brain activation differences between cognitive inhibition and response inhibition.

Regions	R/L	MNI			No.Voxs	Maximum P
		x	y	z		
Cognitive inhibition > Response inhibition						
Occipital Gyrus	L	−28	−68	32	175	0.18
Superior Parietal Lobule	L	−22	−62	42	40	0.15
Response inhibition > Cognitive inhibition						
Inferior Frontal Gyrus	L	−36	22	−12	452	0.21
Inferior Frontal Gyrus	R	48	14	16	29	0.2
Inferior Frontal Gyrus	R	38	24	32	15	0.16
Inferior Parietal Lobule	L	−54	−48	38	10	0.15
Insula	R	30	16	10	312	0.23
Insula	L	−30	18	−8	100	0.23
Middle Cingulate Cortex	R	0	−32	30	93	0.16
Middle Frontal Gyrus	R	32	42	28	430	0.22
Middle Temporal Gyrus	R	50	−30	−2	38	0.17
Putamen	L	−24	12	0	874	0.26
Putamen	R	22	8	−2	436	0.22
Superior Temporal Gyrus	R	56	−22	−4	263	0.18
Supplementary Motor Area	R	12	14	56	291	0.25
Supplementary Motor Area	R	8	−2	60	131	0.2
Supramarginal Gyrus	R	52	−44	34	1295	0.23
Supramarginal Gyrus	L	−64	−44	30	48	0.16

Maximum P is the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size. The coordinates are Montreal Neurological Institute (MNI) standard stereotaxic spaces. The voxel size is 2 mm × 2 mm × 2 mm. R/L, right/left hemisphere.

and left middle frontal gyrus were activated at a significantly lower level in under-aged children and middle-aged adults (Figures 5B,C). Further activated brain areas are reported in Supplementary Table 3.

Brain activation patterns across different age groups for response inhibition

Contrast analyses among different age groups for response inhibition showed that regions with significantly higher levels of activation in adults than under-aged children were located in the bilateral angular gyrus, insula, and right middle frontal gyrus (Figure 5D). Compared to middle-aged adults, the bilateral inferior frontal gyrus and left inferior parietal lobule were activated at a significantly higher level in young adults (Figure 5E), whereas a lower level of activation could be detected in the right inferior frontal gyrus, right inferior parietal lobule, and left middle cingulate cortex in older adults than middle-aged adults (Figure 5F). Further details are reported in Supplementary Table 4.

Validation analysis

The evaluation of the number of experiments contrasting the two subcomponents showed no significant differences between the real contrasts and the randomly selected 54 experiments for response inhibition. The activated brain areas are reported in Supplementary Table 5 and Supplementary Figure 2.

The results from leave-one-out analysis (e.g., leaving out Stroop tasks from cognitive inhibition tasks) were highly consistent with the results of brain activation patterns in each component of inhibitory control derived from MKDA analyses. Further details are reported in Supplementary Tables 6, 7 and Supplementary Figure 3.

Meta-regression and contrast analyses on successful inhibition showed a similar activation pattern of brain regions including the inferior frontal gyrus, supplementary motor area, inferior parietal lobule, insula, angular gyrus, middle cingulate cortex, and occipital gyrus as compared to current MKDA analyses on response inhibition. The activated brain areas and activation maps are reported in Supplementary Tables 8, 9 and Supplementary Figures 4, 5.

Discussion

Applying MKDA and ES-SDM allowed the current meta-analysis to characterize the neural correlates and age-related effects in different subcomponents of inhibitory control. We observed brain areas including the inferior frontal gyrus, insula, middle cingulate cortex, and inferior parietal gyrus being activated in the two subcomponents. Contrast analyses conducted to elucidate the distinct neural substrates for each subcomponent revealed that relative to response inhibition, cognitive inhibition produced stronger activation in the left superior parietal lobule, whereas response inhibition primarily

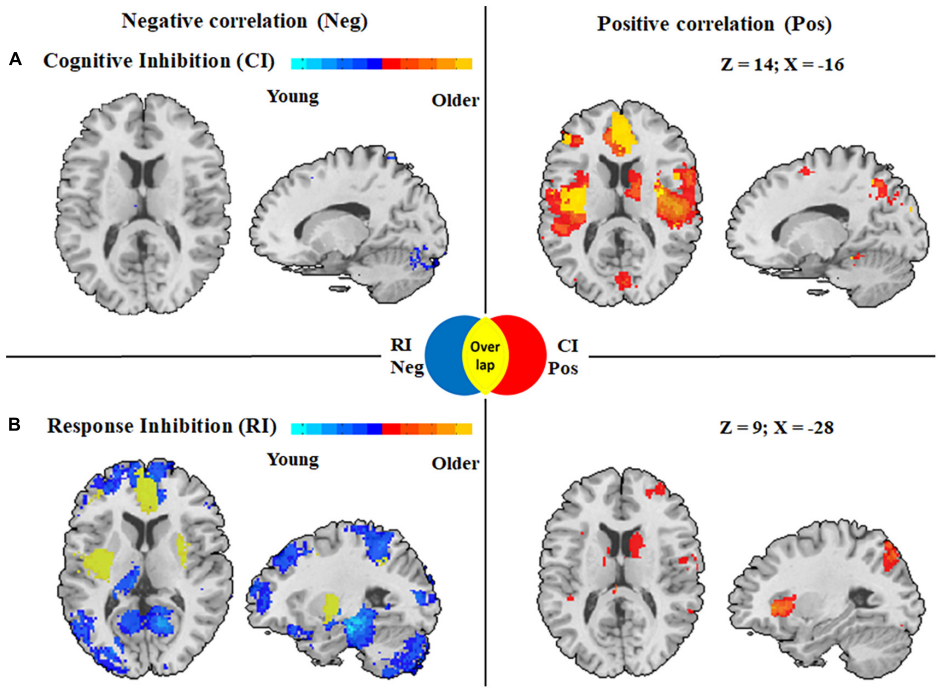

FIGURE 4
Activation maps displaying whole brain regression analysis in cognitive inhibition and response inhibition with age as a covariate. **(A)** Correlation with age with clusters in cognitive inhibition. **(B)** Correlation with age with clusters in response inhibition. Clusters associated with activity in older adults during inhibitory control are displayed in red, whereas clusters associated with activity during inhibitory control among younger adults are displayed in blue. CI Pos: Regions associated with increased activity with aging during cognitive inhibition; RI Neg: Regions associated with decreased activity with aging during response inhibition; Overlap: Regions displayed in yellow derived from overlapping results from regression analyses in two subcomponents with age, meaning a distinct correlation with age in these regions in two subcomponents of inhibitory control.

recruited the right inferior frontal gyrus, insula, middle temporal gyrus, and angular gyrus. Importantly, by performing a meta-regression analysis with age as a continuous variable, we found distinct age-related activation patterns in different subcomponents of inhibitory control in brain regions including the left anterior cingulate cortex, left inferior frontal gyrus, left superior parietal lobule, and bilateral insula. Overall, our results indicated common and distinct neural correlates and distinct age-related activation patterns in the two subcomponents of inhibitory control.

Common neural activation in the two subcomponents of inhibitory control

The MKDA results showed that brain regions including the inferior frontal gyrus, insula, middle cingulate cortex, and superior parietal lobule were activated by both inhibition subcomponents. Therefore, this suggests that the inferior frontal gyrus, insula, middle cingulate cortex, and inferior parietal lobule played the core roles in inhibitory control (Yeo et al., 2011; Choi et al., 2012), which is in line with the findings of previous studies (Cieslik et al., 2015; Lemire-Rodger et al., 2019; Zhang and Iwaki, 2019). Moreover, Hobeika et al. (2016) reported the activation of domain-oriented regions within the inferior frontal gyrus and conflict-detecting regions within the middle cingulate cortex in both inhibition subcomponents, which can be interpreted as showing that either the cognitive inhibition process or response inhibition process involves the process of spatial orientation and conflict detection (Hung et al., 2018).

The main clusters of activation in the two subcomponents of inhibitory control were observed in the followings: (1) the inferior frontal gyrus extending to the insula and (2) the middle cingulate cortex and the superior parietal lobule. The inferior frontal gyrus is known to engage in the process of inhibiting automatic but irrelevant actions while activating task-relevant responses at the same time (Sharp et al., 2010; Wang et al., 2019). Moreover, the activation of the inferior frontal gyrus during detecting changes in stimulus features has also been observed (Dodds et al., 2011). Although the key role of the inferior frontal gyrus in processes of inhibitory control has been reported in a large number of previous studies (Aron et al., 2003; Swick et al., 2011), whether the right and left inferior frontal gyrus play different roles in this process is still subjected to debate. For example, Aron et al. (2003) found

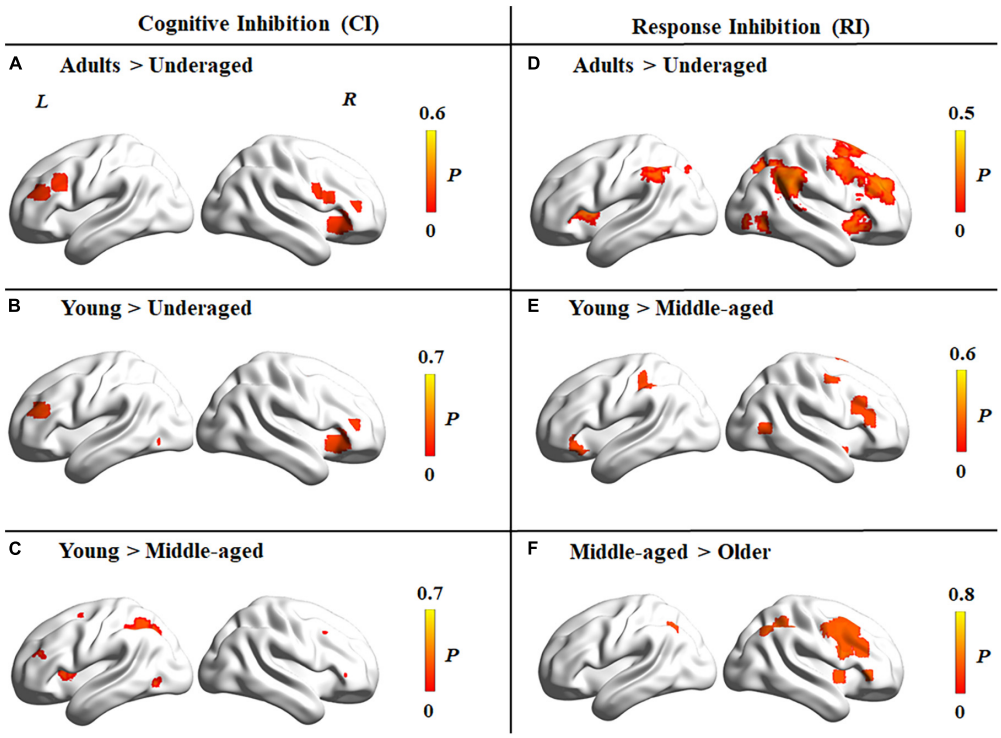

FIGURE 5
Brain activation differences among four age groups for tasks tapping cognitive inhibition and response inhibition. **(A–C)** Brain activation differences in cognitive inhibition. **(A)** Higher activation in adults than under-aged children group. **(B)** Higher activation in young than under-aged children. **(C)** Higher activation in young than middle-aged adults. **(D–F)** Brain activation differences in response inhibition. **(D)** Higher activation in adults than under-aged children group. **(E)** Higher activation in young than middle-aged adults. **(F)** Higher activation in middle-aged than older adults. The color bar represents the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size (P).

that patients with lesions in the right inferior frontal gyrus showed longer stop signal reaction times in stop signal tasks compared with the control group, which might strongly support inhibitory control being executed solely by the right inferior frontal gyrus. Conversely, Swick et al. (2011) found that patients with damage to the left inferior frontal gyrus and insula made more errors than did controls in a Go/NoGo task, which demonstrated that the left inferior frontal gyrus is critical for suppressing prepotent responses. In contrast, this study found that the bilateral inferior frontal gyri were activated during the process of the two subcomponents of inhibitory control. A potential explanation for this is that this study is a meta-analysis study which combined studies using different tasks and stimulus materials. The literature on frontal gyrus function shows that the left inferior frontal gyrus plays a critical role in semantic selection (Thompson-Schill et al., 1998), resolution of interference in semantic memory (Thompson-Schill et al., 2002), and conflicts from representations between incompatible word materials (Milham et al., 2001) during the processes of inhibitory control. Thus, activation of the left inferior frontal gyrus reported by Swick et al. (2011) may partly be due to the letter stimuli used in the Go/NoGo task. In line with this speculatory explanation, the literature included in the current study contained a sufficient number of different paradigms (such as Stroop, Simon, GNG, and SST) and experimental materials (such as picture, arrow, word, letter, sound; see **Supplementary Table 1**), which might partially explain the common activation of the bilateral inferior frontal gyrus during the two subcomponents of inhibitory control reported in the current research.

The anterior insula has been considered as the center that controls brain activity across different tasks and stimulus modalities and regulates inhibitory control mechanisms (W. Cai et al., 2019). Wager et al. (2005) reported a positive correlation between neural activity in the anterior insula and task performance in different inhibitory control tasks. One explanation for this positive correlation is that regions including the anterior insula implement a regulating process that increases with greater input conflict (Miller and Cohen, 2001). Regarding the middle cingulate cortex, studies have revealed that the middle cingulate cortex is the key region for conflict detection in information processing, reallocation of attention resources, and the formation of corresponding actions (Badzakova-Trajkov et al., 2009). When participants were required to perform a

dual task, such as the Stroop task, stronger middle cingulate cortex activation could be observed (Hoffstaedter et al., 2013, 2014; Palomero-Gallagher et al., 2019). Based on the previous findings and the results on the common regions engaged in different inhibitory control tasks, we propose that the inferior frontal gyrus, insula, superior parietal lobule, and middle cingulate cortex may comprise the core neural network of the inhibitory control system.

Additionally, our research found that the right superior occipital gyrus and left middle occipital gyrus were commonly activated in the two subcomponents of inhibitory control, which is in line with the results from previous studies and meta-analyses (Simmonds et al., 2008; Sebastian et al., 2016). Interestingly, Ramautar et al. (2006) indicated that the effect of hyperactivation in the occipital cortex was only present in successful but not in unsuccessful stop trials, which is consistent with the results from validation analyses on successful inhibition contrasts in the current meta-analysis. We speculate that common activation in occipital areas across different types of inhibitory control tasks presumably reflects enhanced visual attention to the inhibition stimuli or conflict interference, considering that the inhibitory control task stimulation used in most of the studies included in our meta-analyses was presented in visual form (refer to **Supplementary Table 1**). Meanwhile, this enhanced activation in the occipital areas may be functionally related to successful inhibitory control, which may be explained by the fact that enhanced visual attention may facilitate the detection of inhibitory signals and thereby contribute to successful inhibitory control.

Distinct neural activation in the two subcomponents of inhibitory control

In this meta-analysis, the inhibitory control paradigms classified as cognitive inhibition required conflict resolution and inhibition of response tendencies for successful responding (Nee et al., 2007). When performing cognitive inhibition tasks (i.e., Stroop, Simon, and Flanker tasks), participants need to actively reorient attention away from a task-relevant stimulus location or feature and then select and initiate an adequate response. Reorienting of attention mainly involves the presupplementary motor area and the superior parietal lobule. The superior parietal lobule plays an essential role in facilitating attention reallocation to characteristics of stimuli and then re-directing attention. Therefore, the significantly stronger activation in the left superior parietal lobule observed in cognitive inhibition compared to response inhibition in the current contrast analysis indicates a higher level of attention reallocation or requirement when performing cognitive inhibition tasks. This thus supports cognitive inhibition depending largely on the inhibition processes of a predominant mental set regulated by goals and conflicts (Nee et al., 2007).

In contrast, for response inhibition, the Go/NoGo and stop signal tasks encompass future action selection and inhibition of a predominant response tendency or an ongoing response, respectively. As mentioned above, the inferior frontal gyrus plays an inhibitory role in resolving conflicts during response execution, and the anterior insula is involved in the regulating process of response inhibition. Thus, there were more activated regions in response inhibition than cognitive inhibition, primarily located in the inferior frontal gyrus and anterior insula. The distinctiveness of response and cognitive inhibition, we suggest, may partly be due to the different cognitive demands in these inhibitory control tasks. Participants are required to resolve conflicts and to involve more sensory or stimulus-related neural activity in cognitive inhibition tasks, whereas the demand for inhibitory control may further increase in response inhibition tasks, which require inhibiting a predominant tendency or stopping of already-initiated actions. Furthermore, these tasks differ in terms of task-related complexity. Suppressing a response tendency or canceling an ongoing action might increase the inhibitory demand as compared to suppressing interference due to irrelevant information or resolving conflicts, as is the case in cognitive inhibition tasks (Sebastian et al., 2013a). As the engagement of the inferior frontal gyrus, middle frontal gyrus and insula play the core roles in the process of inhibitory control, activation in these regions was observed to increase with the increasing demands of inhibitory control tasks in response inhibition.

Interestingly, results from contrast analyses of cognitive inhibition and response inhibition showed a predominantly lateralized differential activation between response inhibition and cognitive inhibition. We hypothesized that the underlying reason may be the different types of stimuli (e.g., letter, word, arrow, and picture) materials used in inhibitory control tasks. By compiling a list of all types of stimulation used in the included literature (refer to **Supplementary Table 1**), we found that more letter-related or text-related stimuli were used in cognitive inhibition tasks, especially the Stroop task, as compared to response inhibition tasks, whereas stimuli including arrows, pictures, or dots were more frequently used in response inhibition tasks. This less verbal nature of the stimuli used in response inhibition tasks compared to cognitive inhibition tasks may ultimately reflect the right-lateralized hyperactivation involved in response inhibition, which is not present in cognitive inhibition.

Age-related changes in activation in subcomponents of inhibitory control

In this meta-analysis, we observed neither a completely coherent increase nor a decrease in the inhibitory network with increasing age in the two subcomponents. In the cognitive

inhibition tasks, activation showed a positive association with age in the anterior cingulate cortex, insula, superior parietal lobule, and inferior frontal gyrus. The results from contrast analyses among different age groups also showed that compared to under-aged children, activation in the inferior frontal gyrus and insula was stronger in adult groups. These age-related changes fit with the existing literature showing that prefrontal regions, including the inferior frontal gyrus and the middle frontal gyrus, become more active with aging (Sebastian et al., 2013b). A previous investigation of neural recruitment involved in cognitive inhibition in children aged 5–10 years reported a higher level of activation in incongruent compared with congruent trials in a network of brain regions supporting cognitive inhibition, including the frontal gyrus and parietal cortex, whereas the activation in the anterior cingulate cortex for incongruent relative to congruent trials decreased with aging (Sheridan et al., 2014). Sheridan et al. (2014) argued that as anterior cingulate cortex plays a specific role in the neural development of cognitive conflict detection and resolution, the decreased activation in the anterior cingulate cortex and general improvement in Simon task performance with aging may suggest that neural recruitment during the process of cognitive inhibition becomes more efficient with aging, which may be related to inhibitory control-related cortical thinning. Moreover, increased activation of task-related regions in the frontal and parietal cortices may reflect the cognitive function underlying cognitive inhibition tasks in younger children developing early but not being fully developed, which means that younger children need to recruit more inhibition-relevant brain regions in the frontal and parietal cortices to improve their performance in cognitive inhibition tasks. Similarly, older adults increasingly recruit additional prefrontal regions to compensate for age-related decline in brain structure and function in cognitive inhibition tasks (Sebastian et al., 2013a). Meanwhile, Nielson et al. (2002) revealed compensational activation in the left prefrontal cortex during cognitive inhibition. These results may support our assumption that a simple cognitive inhibition task requires sufficient functional compensation in the prefrontal regions recruited with aging.

A different pattern of functional age-related changes was found in the response inhibition tasks. We found the activation of the response inhibitory network, including the left anterior cingulate cortex, bilateral inferior frontal gyrus, insula, left superior parietal lobule, and right superior frontal gyrus, was negatively correlated with age. Contrast analyses also showed a linear decline with increasing age in the activation of brain regions including the bilateral inferior frontal gyrus, insula, middle cingulate cortex, and inferior parietal lobule when performing response inhibition tasks. These seemingly differential results might also be explained by the differences in the inhibition processes involved.

In line with a previous study (Reuter-Lorenz and Cappell, 2008), the current findings show that the aging brain fails to recruit additional inhibitory regions with increasing inhibitory demand and a resource ceiling is reached. With increasing task demand, the immaturity of the frontoparietal regions in younger children is associated with an inability to recruit additional inhibition-related brain regions during response inhibition tasks to maintain task performance (Bunge et al., 2002), whereas relative hypoactivation in both the core and expanded inhibitory networks in older adults may further represent a limitation of abilities for flexibly recruiting additional inhibitory networks (Cappell et al., 2010; Schneider-Garces et al., 2010). Prakash et al. (2009) pointed out that the flexibility of the cortical regions becomes limited in older adults with the number of conflicts increasing. It is important to note that the above-mentioned theories have partly been based on the studies investigating age-related differences in working memory. Turner and Spreng (2012) reported differential changes in the activation patterns for the working memory with different cognitive loads and inhibitions with age. Similarly, Sebastian et al. (2013a) showed different activation patterns in the prefrontal regions during inhibition with medium and low inhibition resource demand. Our results and those of these studies indicate that inhibition tasks with high demand might result in limited allocation of cognitive resources in older adults, which can be reflected in declined performance associated with a lower activation of inhibitory networks (Bloemendaal et al., 2018; Billig et al., 2020).

Implications and future outlook

Several neuroimaging studies have contributed greatly to enhancing our knowledge of the neural correlates of subcomponents of inhibitory control or age-related change in the activation in the two subcomponents (Wright et al., 2014; Hung et al., 2018; Zhang R. et al., 2017). However, these studies are limited because of their focus on a restricted age range (Nielson et al., 2002, 2004), their inclusion of a single subcomponent of inhibitory control (Simmonds et al., 2008; Wright et al., 2014; Hu et al., 2018), or their use of a small sample size (Tsvetanov et al., 2018). For example, Simmonds et al. (2008) included only 11 studies in their meta-analysis. It has been argued that to ensure the replicability of a meta-analysis, it should include at least 20 studies (Eickhoff et al., 2016), as otherwise, the conclusions may be questionable. Moreover, Tsvetanov et al. (2018) conducted a study on activity and connectivity differences underlying inhibitory control across the adult lifespan using only response inhibition tasks, including Go/NoGo and stop signal tasks. Hung et al. (2018) reported that unique neural activity was associated with different inhibitory control tasks, but the age-related effects on different types of inhibitory control tasks were unknown. Our meta-analysis addressed these limitations and provided an updated review; thus, our understanding on changes in the neural correlates underlying inhibitory control with aging has been further advanced.

Through synthesizing data from different subcomponents, we found that brain regions including the inferior frontal gyrus and anterior insula, as well as regions including the middle cingulate cortex and supplementary motor cortex, were consistently activated across all inhibition tasks. This finding may suggest that these brain areas are core inhibitory control regions. Meanwhile, different age-related changes in the activation between the subcomponents of inhibitory control could be observed. Functional reorganization of the aging brain in different inhibitory control tasks showed a complex pattern of increase and decline: the corresponding cognitive inhibition tasks required older adults to increasingly recruit the core inhibitory network and additional inhibitory regions, such as the frontal regions and bilateral insula. However, a contrary pattern of age-related decline in the inhibitory network including prefrontal areas and middle cingulate cortex was shown during the process of response inhibition. The current results suggest that these differences might result from the increasing demands on inhibitory function from cognitive inhibition to response inhibition. Furthermore, age-related increased activation of additional inhibitory networks was limited. When the task demand exceeded the older adults' capacity, activation in the inhibitory network decreased clearly. These findings are of significance for the understanding of the neuro-developmental mechanisms of inhibitory control and may provide insights into inhibitory control deficits in clinical settings.

As mentioned above, common and distinct activation patterns are involved in the processes of proactive and reactive inhibition, and age-related changes in activation patterns in proactive and reactive inhibition have been investigated. Experimental evidence from neuroimaging studies supports a right-lateralized frontoparietal circuit being widely recruited through the reactive inhibition process (Yanaka et al., 2010; Gavazzi et al., 2019). In addition, studies currently available on brain substrates of the proactive inhibition process suggest that proactive inhibition seems to rely on a wide network including the presupplementary motor area, right inferior frontal gyrus, and inferior parietal cortex (Aron et al., 2014; Cai et al., 2016). Moreover, Bloemendaal et al. (2016) explored whether age-related neurocognitive deficits in inhibitory control reflect impairments in the proactive inhibition process or reactive inhibition process; they reported that relative to young adults, older adults exhibited impaired reactive inhibition and proactive slowing in the left frontal cortex and cerebellum. Similarly, Kleerekooper et al. (2016) found that with advancing age, the patterns of activation in the right inferior frontal gyrus and motor cortex showed a clear age effect on both proactive and reactive inhibitions. The data collected in the current meta-analysis from stop signal tasks and Go/NoGo tasks to assess response inhibition drew more on proactive than reactive inhibition for suppressing prepotent responses. Although previous studies have not reported a distinct age-related activation pattern of inhibitory control in proactive and reactive inhibitions, the division of inhibitory control in the two subcomponents of cognitive inhibition and response inhibition found in this study is a robust finding on differential age-related activation patterns. However, the heterogeneity of the response inhibition tasks should still be a point of concern for future research.

Methodological considerations

We acknowledge that the current study still has some limitations. First, we note that a potential limitation in meta-analysis methods in general is that any meta-analysis method is prone to publication bias; in this study, we only considered the results available in the published literature and original studies which reported coordinates. Moreover, we could not control the statistical methods used in original articles for thresholding the data. There is an emerging trend to store unthresholded statistical maps, which will allow image-based meta-analyses to be performed in the future studies (Gorgolewski et al., 2015).

The second limitation relates to the bias of employing different tasks for measuring the components of inhibitory control and including studies using a variety of stimulation types. Specifically, our meta-analysis adopted a mixture of inhibitory control tasks as different subcomponents of inhibitory control, such as the Stroop, Simon, and Flanker tasks used to capture cognitive inhibition and the GNG, stop signal task, and antisaccade tasks to capture response inhibition, which consequently increased the heterogeneity of the study designs. Leave-one-out analysis was performed as validation analysis to test homogeneity in cognitive inhibition and response inhibition separately. The results from leave-one-out analysis were consistent with the results of brain activation patterns in each component of inhibitory control from the MKDA analyses and the details are reported in **Supplementary Tables 4, 5** and **Supplementary Figure 3**. Nevertheless, future meta-analyses including additional studies with positive or negative stimulations are needed.

Third, considering that task difficulty and behavioral performance in different inhibition tasks may influence age-related brain activity in different individuals, and not all studies included in the current meta-analysis reported behavioral performance for each participant or task difficulty, we selected a total of 81 studies which reported task performance with successful inhibition in response inhibition tasks. Then, we performed a meta-regression analysis and several contrast analyses separately. The results (refer **Supplementary Tables 8, 9** and **Supplementary Figures 4, 5**) were consistent with the current research, which may confirm the reliability and stability of the current research to a certain extent. However, further considering the study-level task difficulty or behavioral performance reported in each study included in the research is still critical for future meta-analysis.

Fourth, the findings from this study are of significance for the understanding of the neuro-developmental mechanisms of inhibitory control and may provide insights into cognitive health in older adults. However, cognitive health is affected not only by physiological factors such as age, but also by socio-demographic factors; particularly significant is educational attainment. Understanding the links between education and cognitive health or cognitive aging could improve the cognitive prognoses and offer clues about the mechanisms underlying cognitive decline that can be targeted by interventions. Previous studies found that a better level of education might affect cognitive ability in older adults and attenuate aging-related decline in cognition functions (Lövdén et al., 2020; Zahodne and Zajacova, 2020). This may suggest that educational attainment can improve individual behavioral performance in inhibitory control tasks with aging and affect age-related patterns of brain activation during different subcomponents of inhibitory control. Thus, it is critical in the future research to include the level of education as an influencing factor to explore the commonalities or specificity of behavioral performance and age-related patterns of brain activation in inhibitory control tasks between groups with different levels of educational attainment.

Conclusion

In this meta-analysis, we examined the neural correlates of subcomponents of inhibitory control and the difference in age-related changes in activation between the subcomponents. Activation of the middle cingulate cortex, supplementary motor area, inferior frontal gyrus, inferior parietal lobule, and anterior insula was common across the different inhibition processes, which revealed that these regions are the core neural system engaged in inhibitory control. On the other hand, differences in the activation patterns of subcomponents of inhibitory control with aging showed a complex pattern in the functional reorganization of the aging brain. Specifically, when performing cognitive inhibition tasks, stronger activation of the core inhibition regions was observed in older adults, whereas activation in prefrontal areas in older adults declined during response inhibition tasks. We summarize that these differences may be driven by the different demands between inhibitory control tasks. Aging individuals recruit additional inhibition-related brain regions when performing an inhibitory control task. However, with an increasing demand of inhibition tasks, limited reallocation of cognitive resources in older adults eventually results in a lower level of the activation of inhibitory brain regions in older adults during inhibitory control processes. These results may further enhance our knowledge of age-related changes in the activation patterns of inhibitory control and may provide insights into inhibitory control deficits in clinical settings.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The study was reviewed and approved by the Institutional Review Board (IRB) of Southern Medical University.

Author contributions

JL: conceptualization, data curation, data analysis, writing the manuscript, reviewing, and editing. XS, YW, CW, and RH: writing—reviewing and editing. RZ: conceptualization, supervision, funding acquisition, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Nature Science Foundation of China (ref: 31900806). The funding organizations played no further role in study design, data collection, analysis and interpretation, and manuscript writing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.938789/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Mini Review
PUBLISHED 24 August 2022
DOI 10.3389/fnagi.2022.980599

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 28 June 2022
ACCEPTED 04 August 2022
PUBLISHED 24 August 2022

CITATION
Festini SB (2022) Busyness, mental engagement, and stress: Relationships to neurocognitive aging and behavior. *Front. Aging Neurosci.* 14:980599. doi: 10.3389/fnagi.2022.980599

Busyness, mental engagement, and stress: Relationships to neurocognitive aging and behavior

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Considerable research identifies benefits of sustaining mental engagement in older adulthood. Frequent social, mental, and physical activities (e.g., exercise) and lifestyle factors that bolster cognitive reserve (i.e., education, occupation complexity) have been associated with cognitive benefits and delayed onset of dementia. Nevertheless, the relationship between general daily levels of busyness and cognition has been relatively understudied. Open questions remain about whether a causal link exists between a busy lifestyle and mental prowess, the relationship between busyness and stress, and methodological approaches to measure and track busyness levels. Here, the existing evidence is considered, along with future directions for research aimed at characterizing the effects of a busy lifestyle on neurocognitive aging and behavior.

KEYWORDS

busyness, cognitive reserve, aging, stress, cognition, daily activities, memory

Introduction

Extensive evidence indicates that cognition shows deficits with increasing age (see Salthouse, 2009; Park and Festini, 2017, 2018). In particular, fluid cognitive abilities like processing speed and episodic memory show the largest age-related decrements, whereas crystallized abilities like semantic memory (e.g., vocabulary) remain stable or increase with age (Park et al., 2002). Age-related diseases, like Alzheimer's and cerebrovascular disease, also contribute to age-related cognitive deficits, and it can be difficult to differentiate non-pathological aging from underlying pre-clinical disease processes (Sperling et al., 2011). To counteract cognitive deficits associated with advanced age, some research has aimed to identify sources of cognitive preservation in older adulthood. Multiple studies have documented benefits of social, mental, and physical activities

(i.e., exercise; new learning) on cognition and brain health in older adults (e.g., Colcombe et al., 2006; Carlson et al., 2009; Park et al., 2014). Further, lifestyle factors that promote cognitive reserve (Stern, 2002), such as high education and occupation complexity (see Hussenoeder et al., 2019) have been found to be related with better cognitive functioning (e.g., Correa Ribeiro et al., 2013) and lower risk of Alzheimer's disease (e.g., Andel et al., 2005).

However, relatively little research has been conducted to examine the effects of general daily levels of busyness on cognition. Busyness can be defined as having one's time occupied by frequent obligations (Gershuny, 2005). The Martin and Park Environmental Demands Questionnaire (MPED; Martin and Park, 2003) busyness subscale has been used as an assessment of busyness (e.g., Festini et al., 2016, 2019; Kaya et al., 2019). This self-report busyness subscale includes questions like, "*How often do you have too many things to do each day to actually get them all done?*" or "*How often do you rush out of the house in the mornings to get where you need to be?*" Thus, it is distinct from other measures of mental engagement and stress because it specifically assesses busyness and task load. Festini et al. (2016) reported that busier middle-aged and older adults tended to have better cognition, with the strongest relationship observed for episodic memory. This provided an initial demonstration of the potential benefits of living a busy, engaged lifestyle, but much additional research needs to be conducted. It is still unknown whether this relationship is causal–that is, whether or not being busy causes preservation of cognitive abilities, or if the relationship was observed simply because people with better mental function are capable of living busier lives. Moreover, it will be imperative to examine the interaction between busyness, cognition, and stress within the same individuals because it is possible that busyness that becomes stressful may impair cognitive performance, as literature also frequently observes negative consequences of stress on cognitive and brain health (Lupien et al., 2009). Here, I address several important areas for future research, while situating these future studies in the current literature. The focus is primarily on psychological research that addresses "busyness" and "busy lifestyles" directly. Important relevant literature on related concepts regarding mental engagement is briefly considered (for comprehensive reviews see Butler et al., 2018; Bielak and Gow, 2022; Roheger et al., 2022).

Brief review of critical literature

Activity levels

Substantial correlational evidence documents a relationship between heightened activity levels and better cognitive and neural health. Activity level research often implements self-report assessments of a broad range of daily activities, including how often individuals partake in social, physical, and cognitive activities. For example, Seeman et al. (2011) observed that greater social engagement was associated with better episodic memory and executive functioning in middle-aged and older adults. Similarly, Valenzuela and Sachdev (2007) found that individuals with more lifetime experiences, an assessment of intellectual activity across one's lifetime, had less cognitive decline over 18 months. Activity level research has repeatedly documented favorable associations between frequent activities and neurocognitive aging (see Anaturk et al., 2018; Gheysen et al., 2018).

Cognitive reserve, brain maintenance, and STAC-r

The related concepts of cognitive reserve and brain maintenance propose that characteristics like education, occupation complexity, and intellectual challenge can promote maintenance of cognitive function despite brain pathology (e.g., Stern, 2002; Barulli and Stern, 2013; Stern et al., 2020). That is, certain lifestyle factors are proposed to be protective that allow older adults to maintain better overall cognition and delay symptoms of cognitive decline (Soldan et al., 2017; for a review see Song et al., 2022). For example, those individuals with higher education showed more brain atrophy, despite similar cognitive performance (Coffey et al., 1999), suggesting that higher education enables preservation of cognitive faculties despite more pronounced brain pathology. When examining a composite measure of cognitive reserve that included education, occupation, IQ, and intellectual/social activities, Sole-Padulles et al. (2009) observed that cognitive reserve was associated with both larger brain size and increased neural efficiency (cf. Foubert-Samier et al., 2012).

Also considering protective neural enrichment factors, the Scaffolding Theory of Aging and Cognition-revised (STAC-r; Reuter-Lorenz and Park, 2014) proposes that lifestyle factors like education, physical fitness, and multilingualism can promote compensatory neural scaffolding that assists performance. Older adults who have better brain health and who more efficiently use alternate neural resources are proposed to exhibit better cognition and less cognitive decline (see Festini et al., 2018).

Stress and cognition

Much prior research has documented the detrimental effects of stress on neurocognitive function. Non-human animal studies display that unpredictable chronic stress can impair memory, increase anxiety and depressive symptoms, as well as reduce the growth of new neurons in the hippocampus (see Parihar et al., 2011). For instance, Li et al. (2008) exposed mice

to chronic mild stress, such as periods of restricted access to food or continuous light, for 5 weeks, and observed memory disruption. Chen et al. (2010) found that even a 5-h period of acute stress impaired memory, reduced hippocampal dendritic spine density, and disrupted long-term potentiation in mice. Similarly, in humans, stress impairs mental functioning under certain contexts. Oei et al. (2006) observed that stress impaired human working memory performance at high memory loads only (for a review see Martin et al., 2019). The stress hormone cortisol has also been shown to impair memory retrieval of well-learned memories in humans (Wolf et al., 2004). And, literature on burnout finds that uncontrollable stress and feeling over-worked can disrupt not only cognitive performance but also interpersonal interactions and wellbeing (Arnsten and Shanafelt, 2021; Romito et al., 2021).

Nevertheless, some studies report benefits of mild stress. Kofman et al. (2006) observed that undergraduates exhibited superior task-switching and attentional control when anxiety levels were higher at the end-of-the-semester. Some studies also observed that prolonged mild stress can increase neurogenesis in the hippocampus, improve memory, and reduce symptoms of depression and anxiety in rats (Parihar et al., 2011).

Thus, it has been proposed that the relationship between stress and cognition follows an inverted-U pattern (Lupien et al., 2009), such that optimal performance occurs with moderate stress, but that too little or too much stress impairs performance (cf. Yerkes and Dodson, 1908). Perhaps the relationship between busyness and mental functioning follows a similar pattern.

Current research on busyness

Festini et al. (2016) examined the relationship between busyness and cognition in middle-aged and older adults. Those participants who were busier tended to have better processing speed, working memory, reasoning, and crystallized knowledge, with the strongest correlation between busyness and episodic memory. Moreover, busyness accounted for additional variance in all cognitive constructs, even after controlling for age and education.

Notably, these effect sizes between busyness and cognition were small to moderate (magnitudes of 0.16 to 0.32). These effects were observed with a relatively large sample size (330 participants). Thus, in future research, although cumbersome, relatively large samples will be needed to have sufficient power to detect such effect sizes.

Additional busyness research has observed that many, but not all, individuals perceive themselves as busy. Kaya et al. (2019) reported that over three-quarters of their sample of 22- to 54-year-olds characterized themselves as a busy person. Moreover, being busy has been proposed to be a badge of honor, demonstrating high social status and frequent contributions toward society (Gershuny, 2005; Bellezza et al., 2016). Relatedly, research on time shortage perceptions indicates that people often report feeling that they do not have sufficient time to complete what they want to do and feel rushed (Rudd, 2019). A model that considered demographic, personality, health, and activity measures found that busyness was best predicted by younger age, female gender, agreeable and neurotic personality, high levels of need for cognition (i.e., enjoyment of effortful thinking; Cacioppo et al., 1984), and frequent participation in novel activities (Festini et al., 2019).

Related research on retirement has found that partial retirement in the same job negatively impacted cognition, whereas partial retirement with a new employer benefited cognition in those with complex occupations (Mizuochi and Raymo, 2022; cf. Kajitani et al., 2016). This is consistent with the notion that busyness levels drop during retirement, and that new learning at a novel workplace is beneficial to cognition. Interestingly, Atalay et al. (2019) observed similar cognitive decline following retirement, regardless of whether it was forced or voluntary, suggesting that, indeed, the reduction in mental engagement contributes to cognitive decline.

Areas for future research on busyness

Research targeting a causal question

Although methodologically difficult, experimentally manipulating busyness levels is needed to address causality. Currently, only correlational assessments between busyness and cognitive abilities have been performed due to the difficulty of randomly assigning busyness.[1] Nevertheless, lifestyle interventions have been conducted previously with success. See **Table 1** for example intervention studies and their observed benefits (see also Butler et al., 2018; Gomes-Osman et al., 2018). This experimental evidence provides support for use-dependent neural plasticity (e.g., May, 2011; McDonough et al., 2015) and offers a proposed mechanism for why cognition can improve with sustained mental challenge.

To experimentally manipulate busyness, one group of participants could be required to engage in a certain number of tasks for a specified duration/frequency. Pilot studies could determine the optimal number of activities to require,

1 Forced retirement has causality implications too.

TABLE 1 Example lifestyle interventions and their impacts on cognitive health.

Intervention	Citation	Method	Benefits
Synapse project	Park et al. (2014)	New learning: Digital photography, quilting, or both vs. active or passive control groups	Better episodic memory
		14 weeks	
		60–90 yrs	
Synapse project fMRI	McDonough et al. (2015)	High challenge vs. Low challenge Synapse groups; Semantic classification fMRI task	Increased efficiency at modulating brain activity
		14 weeks	
		60–90 yrs	
iPad training	Chan et al. (2014)	iPad tablet computer training	Better episodic memory
		12 weeks	Faster processing speed
		60–90 yrs	
Senior odyssey	Stine-Morrow et al. (2008)	Group-based problem solving of ill-defined problems vs. no-treatment control	Faster processing speed Better inductive reasoning
		20 weeks	Better divergent thinking
		58–93 yrs	
Experience corps	Carlson et al. (2008)	Mentoring elementary school students	Better episodic memory
		Academic year	Improved executive functioning
		60 + yrs	
Experience corps fMRI	Carlson et al. (2009)	Mentoring elementary school students	Improved executive functioning (attentional inhibitory control)
		Flanker task	Increased left prefrontal cortex activity
		6 months	Increased anterior cingulate cortex activity
		60 + yrs	
Aerobic exercise	Colcombe et al. (2006)	Aerobic training versus stretching and toning control	Gray matter increases White matter increases
		6 months	
		60–79 yrs	
Exergame training	Adcock et al. (2020)	Step-based cognitive games, dancing, and Tai Chi vs. control group	Better working memory Improved inhibition
		16 weeks	
		65 + yrs	
Method of loci training	Engvig et al. (2010)	Method of Loci mnemonic training vs. passive control	Better episodic source memory Cortical thickness increases
		8 weeks	
		42–77 yrs	
Juggling training	Boyke et al. (2008)	3-ball cascade juggling vs. control group	Gray matter increases
		3 months	
		50–67 yrs	
Spatial navigation training	Lovden et al. (2012)	Virtual environment spatial navigation training with treadmill vs. treadmill control	Reduced hippocampal shrinking Improved navigation
		4 months	
		20–30 yrs and 60–70 yrs	
Cognitive app training	Bonnechere et al. (2021)	Smartphone/tablet app training	Faster processing speed
		100 sessions	
		60–80 + yrs	

This table is not intended to be an exhaustive list.

by video-tracking or detailed logging of pilot participants' busyness/activity levels.

The key would be to allow participants to choose which activities they perform to keep themselves busy, rather than prescribing activities. Thus, the intervention would manipulate the busyness of the individuals rather than the exact type of tasks. Many prior intervention studies understandably focus on specific tasks, such as exercise (see Gomes-Osman et al.,

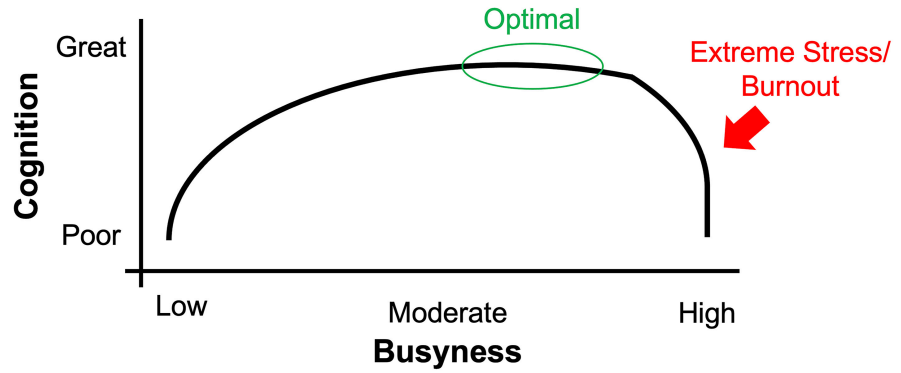

FIGURE 1
Hypothesized inverted-U relationship between busyness and cognition. Additional research is needed to test this proposed relationship. Optimal cognitive performance is predicted with moderate-to-high busyness, before extreme stress/burnout is reached.

2018), volunteering (Musick et al., 1999), or student mentoring (Carlson et al., 2008). Leaving the choice of the activities up to the participants may reduce stress, as enjoyment would likely be higher for self-chosen activities.

The control group may best be designed as a wait-list control group, where participants eventually receive the option to bolster their busyness levels once the control period is complete. A wait-list design would additionally allow researchers to perform analyses within-participants, when the same individual leads a less versus more busy lifestyle. Cognitive abilities would be assessed pre- and post-intervention and compared between the experimental busy group to the non-busy control group/condition.

Interaction between busyness, cognition, and stress

It will also be informative to simultaneously track busyness and stress levels within the same individuals. One individual may find their busy schedule stressful, whereas another may find it enjoyable and fulfilling. Thus, assessing both stress and busyness levels would help determine if busyness is only beneficial if it does not result in a stress response. Indeed, the relationship between busyness and cognition may follow an inverted-U pattern (Yerkes and Dodson, 1908), where moderate levels of busyness are best. See **Figure 1**. One study observed that, in undergraduates, busier participants also reported more stress (Ramsdell and Festini, 2021). Additional work is needed to systematically evaluate the relationship between busyness and stress as it relates to cognition throughout the adult lifespan.

Another aspect worthy of investigation is whether people enjoy the activities that are keeping them busy. One could imagine different types of busy lifestyles–one with activities of their own choosing, and another with obligatory rather than self-selected activities. The type of activities that keep one busy may predict stress. Therefore, future research would benefit from assessing factors such as the enjoyment of, and the type of, activities contributing to busyness.

Busyness, cognitive reserve, and brain reserve

Research devoted to cognitive and brain reserve often uses education, occupation complexity, and IQ as proxies of reserve (e.g., Speer and Soldan, 2015; Franzmeier et al., 2017), the idea being that those with higher levels of education, more cognitively demanding occupations, and higher mental capacity are better able to cope with age-related brain pathology (e.g., Stern, 2002; Richards and Deary, 2005). It may be worthwhile to include assessments of busyness in evaluations of cognitive reserve, as busyness may promote cognitive resources similarly to the existing proxies. For instance, occupation complexity is often coded based on the degree to which one's job requires complex interactions with data (analyzing), people (mentoring), or things (precision working) (Smart et al., 2014). In a similar vein, greater busyness is likely to provide more frequent opportunities for complex daily interactions and new learning, which have been shown to be beneficial (Park et al., 2014; Shors, 2014). Future research could include busyness as a proxy of cognitive reserve, either in isolation, or in conjunction with other measures, as it can provide another window into the complexity of one's life.

Longitudinal assessments of busyness and cognition

Just as influential research has evaluated longitudinal changes in both activity levels and cognition, it may similarly be useful to assess longitudinal changes in busyness and cognition. New or existing longitudinal studies that track cognitive ability or conversion to dementia could add a busyness assessment to determine if there are changes in busyness and cognition across the lifespan within the same individuals. Such longitudinal research is also informative for determining how much variability there is in busyness within an individual over the course of their life. The busiest younger adults may similarly be the busiest older adults. Further, it may be that busyness in young- or middle-adulthood is more beneficial at promoting cognitive reserve and resilience in older age. Such questions remain to be evaluated.

Methodological considerations for the assessment of busyness

Ecological momentary assessments

Ecological momentary assessments (EMAs) offer another promising direction for future research on busyness. Instead of asking people to reflect back, EMAs ask participants to answer questions at the present moment, while they are living their normal daily lives (Shiffman et al., 2008). For example, EMAs ask research participants periodically throughout the day to record what they were doing at that moment. This would provide more quantifiable data regarding the number of tasks that people engage in, as well as the relative proportion of time that was spent during different types of activities. One benefit of EMAs is that they are less prone to recall errors (Shiffman et al., 2008), and would provide more ecologically valid measures of busyness. Kamarck et al. (2007) demonstrated that real-life EMAs of job strain collected at 45-min intervals for 6 days predicted future carotid artery blockage, whereas a global questionnaire did not, providing evidence for the superiority of real-time measurements. Further, EMAs of cognitive abilities, like working memory, have been found to be reliable (Sliwinski et al., 2018), demonstrating the option to assess both busyness and cognition using EMAs in real-life settings.

Additional survey development

While the MPED (Martin and Park, 2003) is a useful tool, it would be beneficial to develop alternate validated self-report assessments of busyness that measure enjoyment of activities, number of different simultaneous obligations, and organized as opposed to rushed busyness. One could imagine a busy life that is scheduled and organized, still with many tasks and obligations, being different than a frantic and hectic busy schedule. Busyness could also be evaluated at different time frames, such as currently, during the last year, etc.

Busyness and age

Busyness in younger adults

Given the paucity of research on busyness in general, it is not surprising that little research has assessed busyness in younger adults. One study observed that undergraduates who were more academically engaged also tended to be more socially engaged, but there was no significant relationship between episodic memory and academic engagement, social engagement, or busyness (Ramsdell and Festini, 2021). It is likely that the relationship between busyness and cognition is weaker in younger than older adults. Several factors contribute to this hypothesis. First, evidence indicates that, on average, younger adults (ages 20–39) live busier lifestyles than older adults (Festini et al., 2019). Further, on average, younger adults have superior cognitive abilities (Park et al., 2002). Thus, the more limited variability in busyness and cognition, and the lower likelihood of neurocognitive decline in younger adults, makes it less likely that strong relationships will exist between busyness and cognition in younger adults.

Busyness and parenthood

Future research should examine differences in busyness for parents versus non-parents. Childrearing adds many daily responsibilities that likely influence busyness levels. It would be worthwhile to evaluate busyness in working and stay-at-home parents and non-parents, including assessment of potential gender differences. Prior research indicates that women tend to be busier (Festini et al., 2019), and, although parent-status was not measured, interestingly, women reported high levels of busyness in the 20s and 30s, whereas men reported *low* busyness in the 20s but high busyness in the 30s, potentially influenced by parenthood (see Verbrugge et al., 1996).

Busyness in older adults

Indeed, the potential beneficial effects of a busy lifestyle are likely most noticeable in older adults, who report lower levels of busyness in general (Festini et al., 2019), and have higher likelihood of cognitive decline due to normal aging or underlying pathology (e.g., McDonough et al., 2020). The beneficial effects of a busy lifestyle may also have the largest impact on the wellbeing of older adults and their families, as finding ways to postpone cognitive decline has truly meaningful impacts.

Discussion and conclusion

Overall, future research on busyness can target many unanswered questions. One critical question will be to test a causal mechanism with an experimental busyness intervention. It will also be valuable to develop additional tools to assess busyness, including EMAs, to measure both busyness and stress within-individuals, and to track busyness longitudinally. Living a busy, yet low stress, lifestyle may be one strategy to boost brain health and is a worthy avenue for additional research.

Author contributions

SF contributed to the conception of the manuscript, performed the literature review, and wrote and edited all sections of the manuscript.

Funding

This study was supported by the University of Tampa Research Innovation and Scholarly Excellence Award/David Delo Research Grant.

Acknowledgments

The author thanks the editor and reviewers for their constructive feedback on this manuscript.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 07 September 2022
DOI 10.3389/fnagi.2022.977191

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 24 June 2022
ACCEPTED 18 August 2022
PUBLISHED 07 September 2022

CITATION
Li W, Sun X, Liu Y, Ge M, Lu Y, Liu X, Zhou L, Liu X, Dong B, Yue J, Xue Q, Dai L and Dong B (2022) Plasma metabolomics and lipidomics signatures of motoric cognitive risk syndrome in community-dwelling older adults.
Front. Aging Neurosci. 14:977191.
doi: 10.3389/fnagi.2022.977191

Plasma metabolomics and lipidomics signatures of motoric cognitive risk syndrome in community-dwelling older adults

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Introduction: Motoric cognitive risk syndrome (MCR) is characterized by subjective cognitive complaints (SCCs) and slow gait (SG). Metabolomics and lipidomics may potentiate disclosure of the underlying mechanisms of MCR.

Methods: This was a cross-sectional study from the West China Health and Aging Trend cohort study (WCHAT). The operational definition of MCR is the presence of SCCs and SG without dementia or mobility disability. The test and analysis were based on untargeted metabolomics and lipidomics, consensus clustering, lasso regression and 10-fold cross-validation.

Results: This study enrolled 6,031 individuals for clinical analysis and 577 plasma samples for omics analysis. The overall prevalence of MCR was 9.7%, and the prevalence of MCR-only, assessed cognitive impairment-only (CI-only) and MCR-CI were 7.5, 13.3, and 2.1%, respectively. By consensus clustering analysis, MCR-only was clustered into three metabolic subtypes, MCR-I, MCR-II and MCR-III. Clinically, body fat mass (OR = 0.89, CI = 0.82–0.96) was negatively correlated with MCR-I, and comorbidity (OR = 2.19, CI = 1.10–4.38) was positively correlated with MCR-III. Diabetes mellitus had the highest ORs above 1 in MCR-II and MCR-III (OR = 3.18, CI = 1.02–9.91; OR = 2.83, CI = 1.33–6.04, respectively). The risk metabolites of MCR-III showed relatively high similarity with those of cognitive impairment. Notably, L-proline, L-cystine, ADMA, and N1-acetylspermidine were significantly changed in MCR-only, and PC(40:3), SM(32:1), TG(51:3), eicosanoic acid(20:1),

methyl-D-galactoside and TG(50:3) contributed most to the prediction model for MCR-III.

Interpretation: Pre-dementia syndrome of MCR has distinct metabolic subtypes, and SCCs and SG may cause different metabolic changes to develop MCR.

KEYWORDS

motoric cognitive risk syndrome, pre-dementia, subjective cognitive complaint, slow gait speed, metabolomics and lipidomics, cross-sectional study

Introduction

Dementia is a chronic disease with high medical cost-burdens to society and now ranks as the 7th leading cause of mortality worldwide (Gauthier et al., 2021). Approximately 55 million people are suffering from dementia, which is estimated to increase to 152 million in 2050 (Gauthier et al., 2021), although less than 25% globally are diagnosed, especially as low as approximately 10% diagnosis rates in the lower-income countries (Semba et al., 2020; Gauthier et al., 2021). Dementia has a long preclinical stage of several years to decades before subtle cognitive alterations are detectable (Semba et al., 2020). Early identification of the increased risk individuals for future dementia, may offer timely treatment, since disease-modifying strategies for dementia like Alzheimer's disease are almost unavailable worldwide. Motoric cognitive risk syndrome (MCR), characterized by subjective cognitive complaints (SCCs) and slow gait speed (SG) in the absence of mobility assistance and dementia, was first proposed and validated as a pre-dementia syndrome in 2013 by Verghese et al. (2012, 2014). The prevalence of MCR was 10% in older adults worldwide (Maggio and Lauretani, 2019; Meiner et al., 2020).

Motoric cognitive risk syndrome has received increasing attention (Verghese et al., 2012, 2013; Ayers and Verghese, 2016; Wang et al., 2016; Maguire et al., 2018), and previous studies provide figures and data further justifying this pre-dementia syndrome. In a study consisting of 26,802 samples has showed that MCR increases two-fold incidence of cognitive impairment (aHR 2.0) (Verghese et al., 2014). MCR increases the incidence of falls and post-fall fractures (Beauchet et al., 2019), hospitalization, disability (Doi et al., 2017), and mortality in older adults (Yuan et al., 2021). MCR patients have poorer performance in global cognitive performance by the Mini-Mental Status Examination, Free and Cued Selective Reminding Test, Frontal Assessment Battery and Trail Making Test parts A and B (Sekhon et al., 2017; Maguire et al., 2018). The risk factors of MCR include aging, low education, cardiovascular diseases, obesity, physical inactivity, anxiety-depressive disorders (Meiner et al., 2020), small cerebral vessel diseases (Wang et al., 2016), and frailty (Sathyan et al., 2019). Increased levels of interleukin-6 and C-reactive protein have also been observed in MCR patients (Bortone et al., 2021). Compared with healthy controls, MCR patients have lower gray matter volume in the prefrontal and premotor cortexes, and higher levels of lacunar lesions in the frontal lobe (Sekhon et al., 2019), which are related to motor planning and modulation (Blumen et al., 2019).

Previous studies indicated that the dysregulation of specific lipids and amino acids is associated with cognitive declines (Semba et al., 2020). However, the metabolomics and lipidomics disorders caused by MCR is still less studied. Here, we performed plasma metabolomics and lipidomics investigations on MCR, preliminarily providing insights into MCR metabolic mechanisms and signatures.

Materials and methods

Study design of the West China Health and Aging Trend cohort study and the sample selection

This was a cross-sectional study, and the data came from the ongoing prospective West China Health and Aging Trend cohort study (WCHAT), which was initiated in 2018. The Ethical Review Committee of West China Hospital approved WCHAT [Permission number: 2017(445)], and it was registered on the Chinese Clinical Trial Registry [ChiCTR1800018895] (Hou et al., 2021). All procedures were conducted along the principles of the 1964 Declaration of Helsinki guidelines and its amendments. In brief, WCHAT originally recruited 7,536 community-dwelling residents. Most of the participants were over 50 years old, 37.47% were males, and 62.53% were females.

Specifically, the WCHAT study recruited 7,536 community residents. After excluding 60 persons under 50 years old, 22 people with dementia or severe cognitive impairment, 617 individuals with ADL assistance and 806 persons with missing MCR diagnostic information, 6,031 participants were finally

retained for subsequent epidemiological analysis. This study included 577 plasma samples for metabolomics analysis from participants who were willing to attend the follow-up visit, and the subjects with severe diseases were excluded. Moreover, to ensure the reliability of the metabolomics and lipidomics analysis, we recruited as many subjects with MCR as possible.

Evaluation of motoric cognitive risk syndrome

The operational definition of MCR was the presence of SCCs and SG but without dementia or mobility disability, as proposed and validated by Verghese et al.'s (2012, 2014), Maggio and Lauretani (2019), and Stephan et al. (2020). The diagnosis of present MCR was described elsewhere in detail (Sun et al., 2022). Dementia was identified by self-and/or proxy-reported previous diagnoses by physicians. Additionally, we excluded probable dementia which was classified as severe cognitive impairment using the 10-item Short Portable Mental Status Questionnaire (SPMSQ) (Pfeiffer, 1975). Mobility disability was defined by Activities of Daily Living (ADLs) assistance. The SCCs were based on standardized questionnaire items: (1) the Geriatric Depression Scale (GDS): "Do you feel that you have more problems with memory than most?" (endorsed response: yes) (Stephan et al., 2020); (2) In the past month, have memory problems affected your daily activities? (endorsed response: yes). Gait speed was obtained by measuring the normal pace of walking speed over 4 m. SG was determined by having a walking speed greater than or equal to 1 standard deviation (SD) below the average of age- and sex-specific values, to overcome population and program variability (Capistrant et al., 2014). The present cognitive impairment group (CI) was defined as having mild or moderate cognitive impairment by the SPMSQ (Pfeiffer, 1975).

Metabolomics and lipidomics

Trained professionals collected three tubes of fasting peripheral blood from participants in the morning. Routine blood tests were performed on the same day. The plasma samples were centrifuged at 14,000 g at 4°C for 20 min, and the supernatants were used to extract hydrophilic metabolites and lipids. $^{13}C_6$ L-Lysine hydrochloride powder (Silantes) and $^{13}C_6{}^{15}N_4$ L-Arginine hydrochloride powder (Silantes) were used to monitor the extraction efficiency of hydrophilic metabolites. PE (16:0-D31-18:1) was used to monitor the extraction efficiency of lipids. The hydrophilic metabolites were extracted with pre-cooled methanol (Yuan et al., 2012), while the lipids were extracted according to the method of Bligh and Dyer (1959).

Untargeted metabolomics and lipidomics were carried out at the Facility Center of Metabolomics and Lipidomics of Tsinghua University (Patti et al., 2012; Hakimi et al., 2016; Tang et al., 2016). A BEH amide column (Waters, United States) and a BEH C18 column (Waters, United States) were used for metabolomics analysis under positive and negative ion modes, respectively. A CORTECS C18 column (Waters, United States) was used for lipidomics under positive mode. Pooled quality controls (QCs) were inserted for every 15–20 injections of plasma samples. Polar metabolites were assigned using Tracefinder (Thermo, CA, United States) based on an in-house database. Standard MS/MS spectra of over 1,500 metabolites were included in the database. Lipids were identified using Lipidsearch (Thermo, CA, United States) software. Only lipids with reliable MS/MS were used for the following statistical analyses.

Bioinformatics analysis

The metabolites and lipids were extracted in the same batch. Moreover, the samples were continuously analyzed by mass spectrometry. Some metabolites were deleted, including those with missing values NA >20% and CV (Coefficient of Variation of QC samples) >30%. To normalize the metabolite intensity, we first calculated the average total intensity of all samples, and then divided the total intensity of each sample by the average total intensity of all samples to get a coefficient. Finally, the measured intensity of each metabolite was divided by the coefficient for the corresponding sample to obtain the normalized intensity of each metabolite in that sample. The lipidome and the metabolome data obtained in positive acquisition mode, and the metabolome data obtained in negative acquisition mode, were filled the blank with half of the minimum intensity of metabolites in all samples. The intensity values were log2-transformed to reduce skewness and stabilize the variance. Statistical analyses were conducted using R version 4.1.0 or SPSS software version 26 (IBM Corporation, Chicago, IL, United States).

The Kolmogorov-Smirnov test was used to test the normal distribution of the continuous variables, while the Mann–Whitney *U* test was utilized for difference analyses and the median ratio value was calculated, when the metabolomic and lipid data were abnormally distributed ($p < 0.05$). Logistic regression was used for risk analysis adjusted for sex and age. Linear regression was used for the correlation of continuous variables. The Kruskal-Wallis test was used for the comparison of multiple groups. Consensus clustering of metabolomics and lipidomics data was carried out to determine the metabolic subtypes of participants with MCR (R package: ConsensusCluster Plus). Lasso was used to select metabolic characteristics and establish a regression model to predict MCR-III. A 10-fold cross-validation was performed, and the minimum

lambda value plus standard error was selected as the best lambda to solve the model overfitting problem (R package: glmnet, *s* = lambda.1 s). The contribution of each metabolite in each prediction model was defined by the coefficient: Contribution = abs(coefficient)/sum[abs(coefficient)] (Liang et al., 2020).

Results

Epidemiological and clinical features of motoric cognitive risk syndrome

The overall prevalence of MCR was 9.7% (n = 582), while 15.4% (n = 929) of participants suffered from CI. In the clinical subgroups, 454 participants (7.5%) were diagnosed with MCR-only, 801 (13.3%) with CI-only, 128 (2.1%) with concurrent MCR and CI (MCR-CI), and 4,648 participants (77.1%) without MCR or CI (Neither) (**Figure 1A**). Overall, CI patients constituted 22.0% of MCR, while MCR patients accounted for 13.8% of CI, which were in line with other studies (Sekhon et al., 2017). In demography, the mean ages sequentially increased among Neither (61.7 ± 8.1), MCR-only (64.1 ± 7.7), CI-only (64.4 ± 8.9) and MCR-CI (66.9 ± 9.1) groups, while the marriage rates successively decreased. Female numbers prevailed in the four groups (**Figure 1B** and **Supplementary Table 1**). The prevalence of MCR and CI significantly differed by ethnicity (**Supplementary Table 1**) (Liu et al., 2020). Additionally, the distribution of a group of biological and clinical factors was significantly divergent among the Neither, MCR-only, CI-only and MCR-CI groups (**Supplementary Table 1**). Multiple logistic regressions adjusted for age and sex were further analyzed. The significantly correlated factors with specific subgroups differed among the MCR-only, CI-only and MCR-CI groups. Low activity, obesity, low handgrip strength, diabetes mellitus and stroke were positively associated with MCR-only, while cholesterol and high-density lipoprotein (HDL) were negatively associated with it. For CI-only, it had positive associations with low activity, malnutrition risk, and depression. Similar to CI-only, we found that MCR-CI was positively correlated with low activity, low handgrip strength, malnutrition risk and depression (**Figure 1C**), in agreement with the previous reports (Beauchet et al., 2020).

To verify whether MCR had a higher incidence of CI than the healthy Neither group, we partially completed the 4-year follow-up of WCHAT in 2021, and 1983 participants were available for epidemiological analysis. We found that the prevalence of MCR-only, CI-only, and MCR-CI was higher in 2021 than in 2018 (**Figure 1D**). Moreover, the incidence of CI (13.58%) in MCR-only people was higher than that (11.23%) in Neither group, which was initially healthy people in 2018 (**Figure 1E**).

Metabolic characterization of motoric cognitive risk syndrome

To investigate the metabolic characteristics of MCR, metabolomics and lipidomics profiling were carried out in 577 plasma samples, with 82 in MCR-only, 66 in CI-only, and 19 in MCR-CI. In total, we identified 345 hydrophilic metabolites and 231 lipids. PCA of the metabolome and lipidome data of the samples and the QCs showed high data quality (**Figures 2A,B**). Logistic regression analysis of the metabolites after adjusting for sex and age identified 24, 72, and 45 differential metabolites in the MCR-only, CI-only, and MCR-CI groups, respectively ($p < 0.05$). All risk metabolites of MCR-only and the top 25 risk metabolites of CI-only and MCR-CI were shown in **Figures 2C–E** and **Supplementary Tables 4–6**. L-Proline (OR = 1.46, CI = 1.15–1.85), and L-cystine (OR = 1.37, CI = 1.06–1.79) were positively associated with MCR-only, while asymmetric dimethylarginine (ADMA) (OR = 0.67, CI = 0.51–0.88), and N1-acetylspermidine (OR = 0.69, CI = 0.53–0.88) were negatively associated with it. Triglycerides (TG, 50:2) (OR = 1.71, CI = 1.27–2.32) and hexylresorcinol (OR = 0.55, CI = 0.40–0.73) had the highest and the lowest ORs for CI-only, respectively. For MCR-CI, TG (52:2) was the only positively correlated, and PE(38:3) had the lowest OR. Further overlapping analysis showed that the risk metabolites of MCR-only were different from those of CI-only and MCR-CI, but the metabolic changes induced by MCR-CI and CI-only were relatively closer (**Figure 2F**). This indicated that MCR-only had a distinct metabolic profile.

Metabolic stratification of motoric cognitive risk syndrome

Omics studies show that the same diagnosed diseases may have distinct molecular profiles (Mapstone et al., 2014). To identify whether MCR-only has distinguishing metabolic subtypes, we performed unsupervised clustering analysis using the top 25% most variable metabolites (144 metabolites) from 576 metabolites of 82 MCR-only participants. Consequently, three subtypes, MCR-I, MCR-II, and MCR-III were identified. Multiple logistic regression further verified the clinical discrepancy of these metabolic MCR subtypes compared with healthy participants without MCR and CI (**Supplementary Table 3**). The three subtypes shared five factors with the ORs all below 1, including body mass index (BMI), short physical performance battery (SPPB) score, skeletal muscle mass, total body water and body minerals. Among them, the factor of body minerals had the highest protective association with these three subtypes, with ORs all below 0.3. Body fat mass (OR = 0.89, CI = 0.82–0.96) was negatively correlated with MCR-I, and comorbidity (OR = 2.19, CI = 1.10–4.38) was positively correlated with MCR-III. Diabetes mellitus had

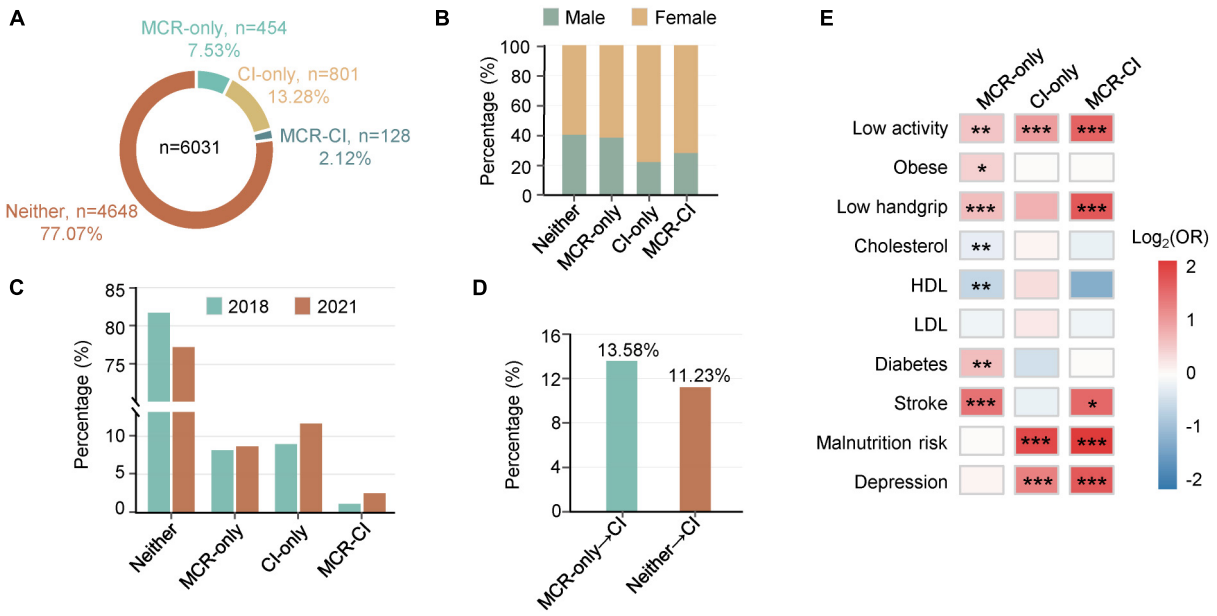

FIGURE 1
Epidemiological statistics of motoric cognitive risk, cognitive functional impairment and comorbid motoric cognitive risk-cognitive functional impairment. **(A)** A statistical analysis of the West China Health and Aging Trend study (WCHAT). 7.53% MCR-only, 13.28% CI-only, 2.12% MCR-CI participants in WCHAT (n = 6,031). **(B)** Percentage of men and women in Neither, MCR-only, CI-only, MCR-CI. **(C)** Heatmaps showing associated factors for MCR, CI, and MCR-CI. Red represents positive risk and blue represents negative risk. Significance is indicated by "*"(*0.01 < p < 0.05, **0.001 < $p \leq$ 0.01, ***$p \leq$ 0.001). **(D)** A statistical analysis of 1983 participants with MCR-only, CI-only, and MCR-CI in 2018 and 2021. **(E)** Incidence comparison between MCR-only and Neither for CI in the fourth year of follow-up.

the highest ORs for MCR-II (OR = 3.18 CI = 1.02–9.91) and MCR-III (OR = 2.83 CI = 1.33–6.04) but it was not significant for MCR-I.

To identify metabolic disparities among the three subtypes, we screened out the differentially changed metabolites using the Kruskal-Wallis test. A total of 124 metabolites were significantly different among the three subtypes (False Discovery Rate (FDR) <0.05) (Figure 3A), and consensus clustering was used to divide them into four groups according to the patterns of changes. The levels of triglycerides, which occurred mainly in group 1 and group 4, were reported to be closely associated with cognitive regulation (Figure 3B) (van der Lee et al., 2018). In particular, triglycerides in group 1 were highly expressed in MCR-III (Figure 3A), and the total carbon number of most of these triglycerides was less than 53 (Figure 3B). In contrast, triglycerides in group 4 were highly expressed in MCR-I and MCR-II (Figure 3A), and the total carbon numbers of most of them were above 54 (Figure 3B). Besides, more triglycerides, such as TG(56:9), TG(58:5), and TG(58:6), contained unsaturated side chains in group 4, which is consistent with previous findings that long-chain polyunsaturated triglycerides (PUTGs) were significantly reduced in the precursor stage of mild cognitive impairment (MCI) and the reduction in PUTGs may be related to the early changes in AD (Bernath et al., 2020). Group 2 was higher in MCR-III, with metabolites including sphingomyelin and ceramides. Elevated serum sphingomyelin and ceramide levels have been reported to be associated with an increased risk of AD (Wong et al., 2017). Aromatic amino acids and steroids accounted for a large proportion in group 3 (Figure 3B).

Identification of the most harmful motoric cognitive risk syndrome subtype and metabolites

To identify the metabolic characteristics unique to the three subtypes, especially MCR-III, we performed logistic regression analysis within the MCR subtypes. Taking the healthy Neither group as a reference, we identified 65 risk metabolites for MCR-I, 75 for MCR-II, and 74 for MCR-III (Supplementary Tables 7–9).

To determine the relationship between MCR subtypes and cognitive impairment, we, respectively screened the metabolites showing differences between MCR subtypes and CI-total (which contains MCR-CI and CI-only) using the Mann–Whitney U test. The metabolic and lipidomic features of MCR-III were relatively more correlated with CI-total than MCR-I and MCR-II (Figures 3C–E), suggesting that metabolic MCR-III may exacerbate cognitive decline and dementia more than other subtypes.

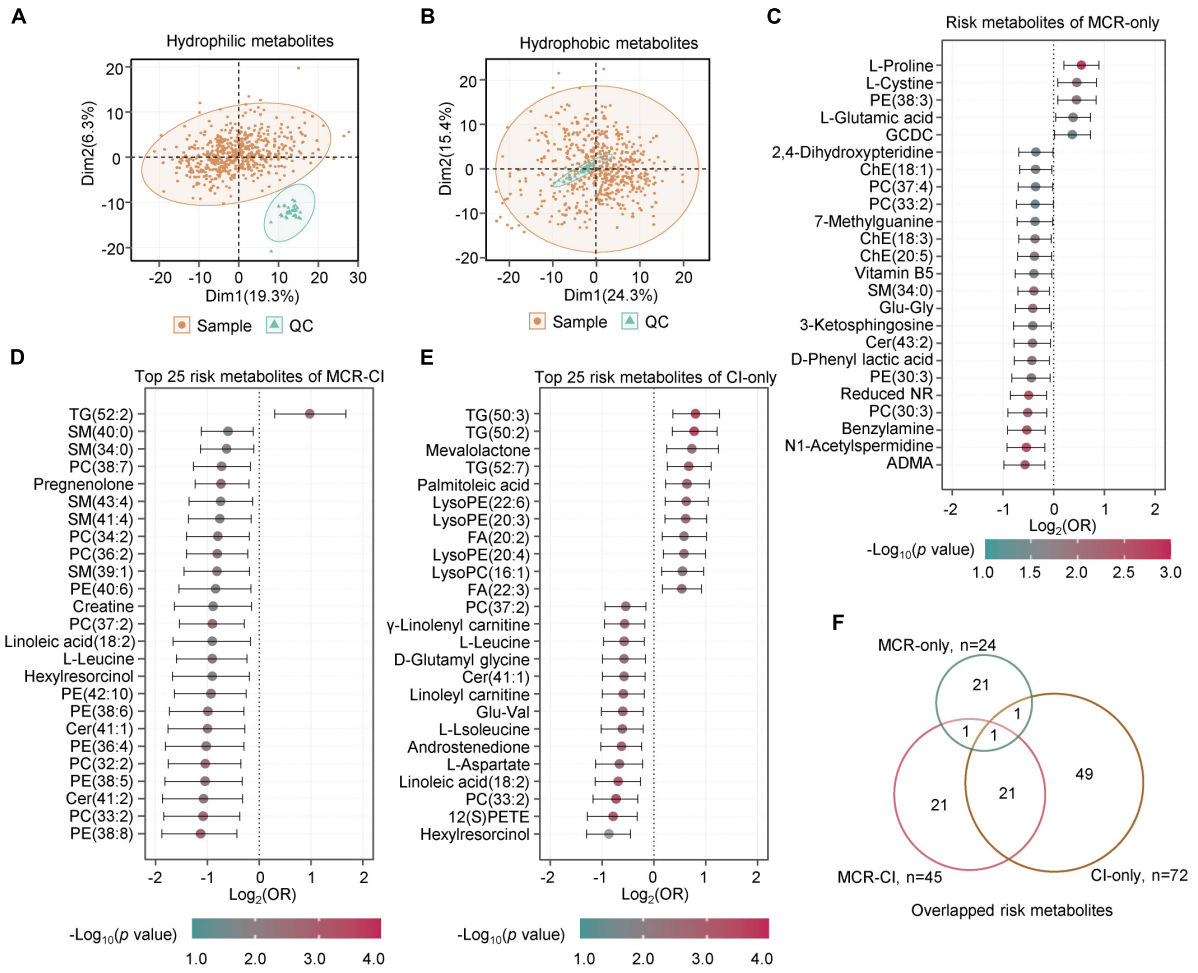

FIGURE 2
The metabolites with significant differences in motoric cognitive risk, cognitive functional impairment and comorbid motoric cognitive risk-cognitive impairment. **(A)** PCA of the metabolome of samples and quality controls (QCs). **(B)** PCA of the lipidome of samples and QCs. **(C)** The forest map showing the risk metabolites of MCR-only by logistic regression analysis ($p < 0.05$). There were 5 positive risk metabolites and 19 negative risk metabolites. **(D)** The forest map showing the top 25 risk metabolites of MCR-CI by logistic regression analysis ($p < 0.05$). There was 1 positive risk metabolite and 24 negative risk metabolites. **(E)** The forest map showing the top 25 risk metabolites of CI-only by logistic regression analysis ($p < 0.05$). There were 11 positive risk metabolites and 14 negative risk metabolites. **(F)** Overlapping analysis of risk metabolites of MCR-only, CI-only and MCR-CI. The metabolites in panels **(C–E)** are ranked by the crude odds ratios (OR). The segment of each metabolite means 95% CI. Cer, ceramide; PC, phosphatidylcholine; LysoPC, lysophosphatidylcholine; PE, phosphatidylethanolamine; LysoPE, lysophosphatidylethanolamine; TG, triacylglycerol; SM, sphingomyelins; FA, fatty acid; ChE, cholesterol ester; GCDC, glycochenodeoxycholic acid; ADMA, asymmetric dimethylarginine; Reduced NR, 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide.

Overlapping analysis showed that 28 risk metabolites were unique to the MCR-III subtype (Figure 4A). Next, we developed a specific metabolic model to identify MCR-III participants out of all MCR individuals. A random sampling of 50 discovery sets (70% of samples) with replacement, and feature selection from 28 metabolic features unique to MCR-III, were used to build LASSO regression models, which showed the best 10-fold cross-validation performance for a given phenotype in the cohort. We ran the model built in the discovery sets with the remaining MCR participants as verification sets (n = 25), to measure the independent performance of the metabolic model. Among the 50 random metabolic models, the mean receiver operating characteristic (AUROC) of the discovery sets was 0.9599 (AUC range: 0.9000–0.9975), and the mean AUROC of the verification sets was 0.8799 (AUC range: 0.7403–0.9936) (Figures 4B,C).

When the value of λ was one standard error plus the minimum value, we analyzed the contribution of these metabolites in the model. The metabolites of PC(40:3), SM(32:1), TG(51:3), eicosanoic acid(20:1), methyl-D-galactoside and TG(50:3) performed well and contributed robustly in most of the 50 models (Figure 4D). Thereby, these six metabolites can be used as key metabolites to distinguish MCR-III from other MCRs. Then, we used them as eigenvalues to establish a ridge regression model to predict MCR-III and not

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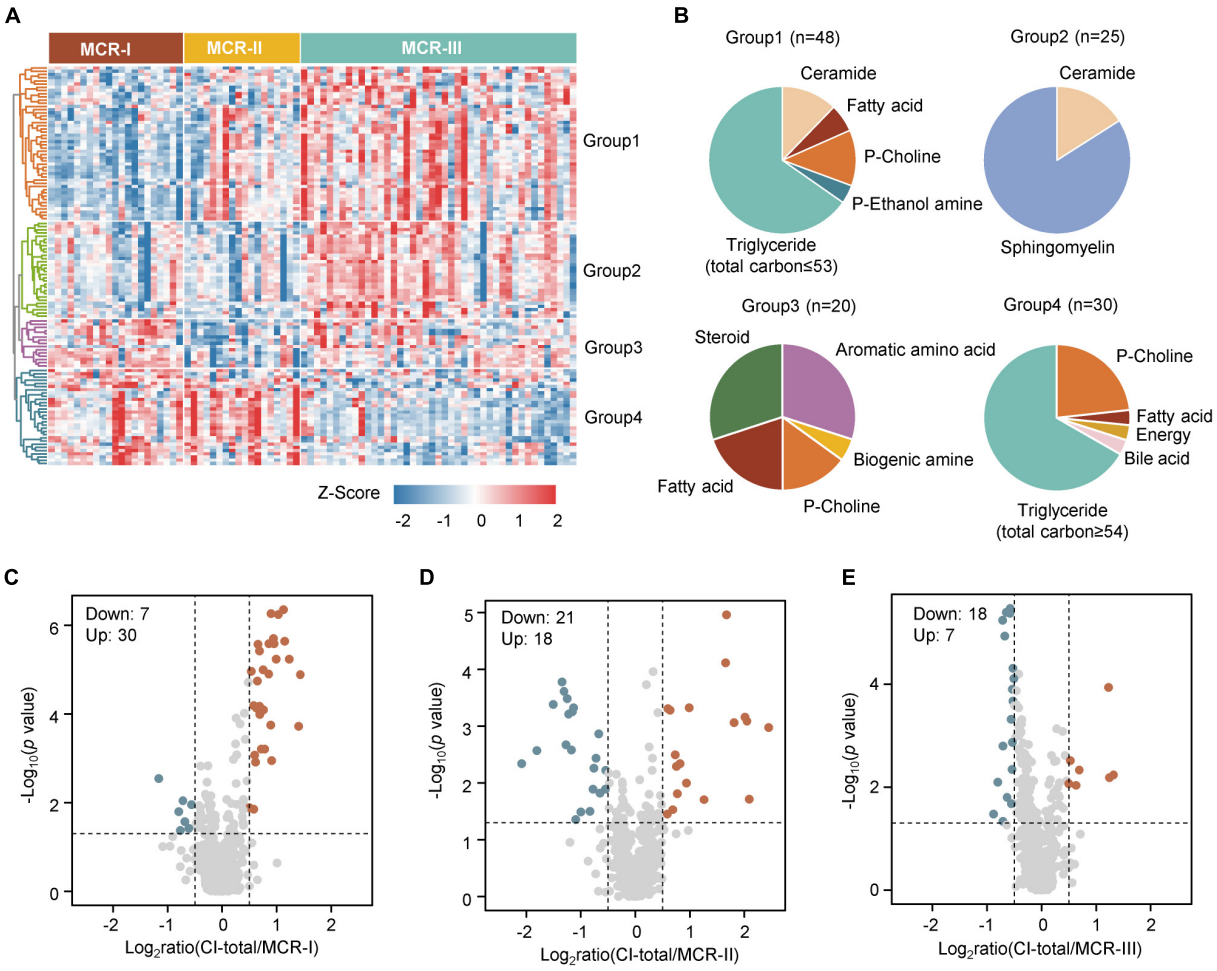

FIGURE 3
Three metabolic subtypes of MCR. **(A)** The heatmap shows the relative abundance (z score transformed) of the significantly changed metabolites in three clusters (Kruskal-Wallis test, FDR <0.05). **(B)** Classification of metabolites into four groups. **(C)** The significantly changed metabolites in both CI-total and MCR-I (Mann–Whitney *U* test, $p < 0.05$, Log_2ratio >0.5 or Log_2ratio <−0.5). **(D)** The significantly changed metabolites in both CI-total and MCR-II (Mann–Whitney *U* test, $p < 0.05$, Log_2ratio >0.5 or Log_2ratio < −0.5). **(E)** The significantly changed metabolites in both CI-total and MCR-III (Mann–Whitney *U* test, $p < 0.05$, Log_2ratio >0.5 or Log_2ratio <−0.5).

MCR-III. As above, 50 different discovery sets were randomly selected to build 50 models. We found that the accuracy of the model's predictions was greatly improved. The mean AUROCs value of both discovery sets and verification sets was above 0.9, and the best AUROC value was above 0.98 (Figures 4E,F).

Metabolic features associated with subjective cognitive complaint and slow gait

Subjective cognitive complaints and SG are two key components used to evaluate MCR. We assumed that the MCR subtypes might have metabolic features similar to those of SCCs and/or SG. To determine the association between MCR subtypes and SG, we screened metabolites closely related to walking speed. Linear regression analysis was adjusted for sex and age. A total of 69 metabolites changed significantly with the alteration of gait speed, of which 58 were positively correlated and 11 were negatively correlated with gait speed (Figure 5A). The 69 risk metabolites of SG could be classified into ten categories (Figure 5B). Among them, sphingomyelins, p-choline, ceramides, steroids, glycerophospholipids and nucleotides increased with speed, while diglycerides decreased with speed (Figure 5D). Overlapping analysis revealed the largest number of common risk metabolites between SG and MCR-II (Figure 5C). Notably, four risk metabolites of SG, Hex1Cer(41:1), SM(38:3), SM(36:0), and SM(32:1), were also risk metabolites of MCR-III.

Similarly, the logistic regression analysis revealed 13 metabolites associated with SCCs, of which seven were positive and six were negative correlations (Figure 6A). When

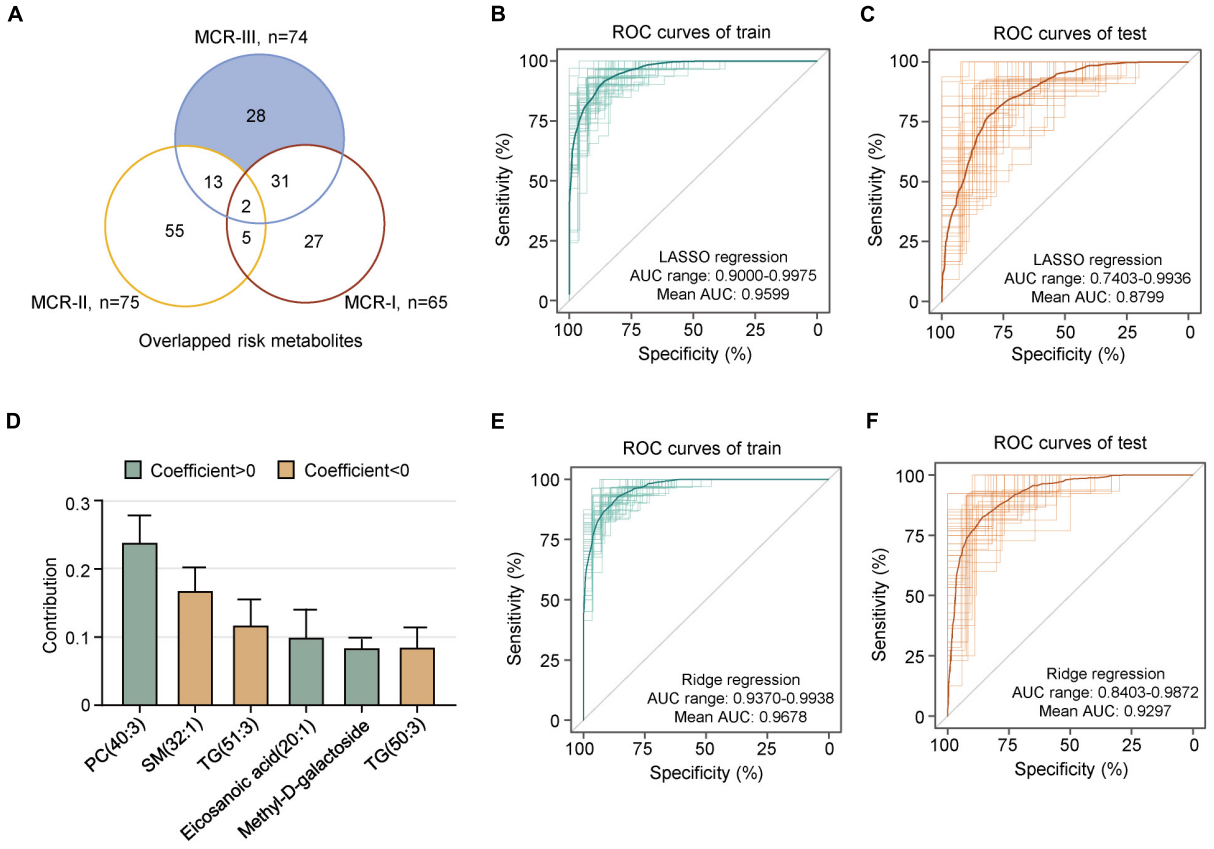

FIGURE 4
A metabolic model predicts MCR-III. **(A)** Overlapping risk metabolites of MCR-I, MCR-II and MCR-III. Shaded in blue are the risk metabolites specific to MCR-III, which were used in subsequent modeling. **(B)** The 50 ROC curves of the training sets in lasso regression; the bold one is the mean AUC of 50 times. **(C)** The 50 ROC curves of the test sets in lasso regression; the bold one is the mean AUC of 50 times. **(D)** Contribution of the six metabolites to the prediction model of MCR-III or no. The error bar represents a 95% CI. **(E)** The 50 ROC curves of the training sets in ridge regression; the bold one is the mean AUC of 50 times. **(F)** The 50 ROC curves of the test sets in ridge regression; the bold one is the mean AUC of 50 times.

comparing them with the metabolites of MCR subtypes, we found two overlapping metabolites between SCC and MCR-I, none between SCCs and MCR-II, and four between SCCs and MCR-III (**Figure 6B**). In detail, these four compounds were 2,5-dihydroxybenzoic acid, oleamide, arachidonic acid(20:4) and myristoleic acid (14:1). It is well known that subjective cognitive complaints (SCCs) are currently considered a major feature of mild cognitive impairment (MCI) (Mitchell, 2008). However, only three common risk metabolites of CI and SCCs have been found. We assume that SCC may not be severe enough to cause significant metabolic alterations. As a result, we only obtained 13 risk metabolites for SCC. In contrast, 75 risk metabolites were obtained for CI.

Discussion

Motoric cognitive risk syndrome, with the two components SCCs and SG, is a stronger predictor of the cognitive decline and dementia than either measure alone (Verghese et al., 2014). Subjective cognitive complaints (SCCs) and slow gait speed (SG) are two early indications of cognitive decline and dementia (Semba et al., 2020). SCCs probably precedes MCI by up to 15 years (Reisberg et al., 2008), while the occurrence of the decline in gait speed is 12 years ahead of MCI (Buracchio et al., 2010). The pooled hazard ratios (HR) of MCR were 1.5 to 2.7 for cognitive impairment and 1.9 to 3.27 for dementia (95% CI, 1.75–2.39) (Verghese et al., 2012, 2014), but not all MCR will develop into MCI, dementia, or even AD (Semba et al., 2020). It has been reported that the prevalence of MCR varied in different countries and/or regions, with 8.0% in Europe, 6.3% in Japan and 7.0% in United States (Maggio and Lauretani, 2019). The overall MCR prevalence of 9.7% in the present study was in line with the pooled global prevalence of 9.7% estimated from 26,802 participants across 17 countries (Verghese et al., 2014).

Metabolomic platforms potentiate the detection of hundreds of metabolites for the discovery of disease phenotypes. However, multi-omics platforms have been barely used for

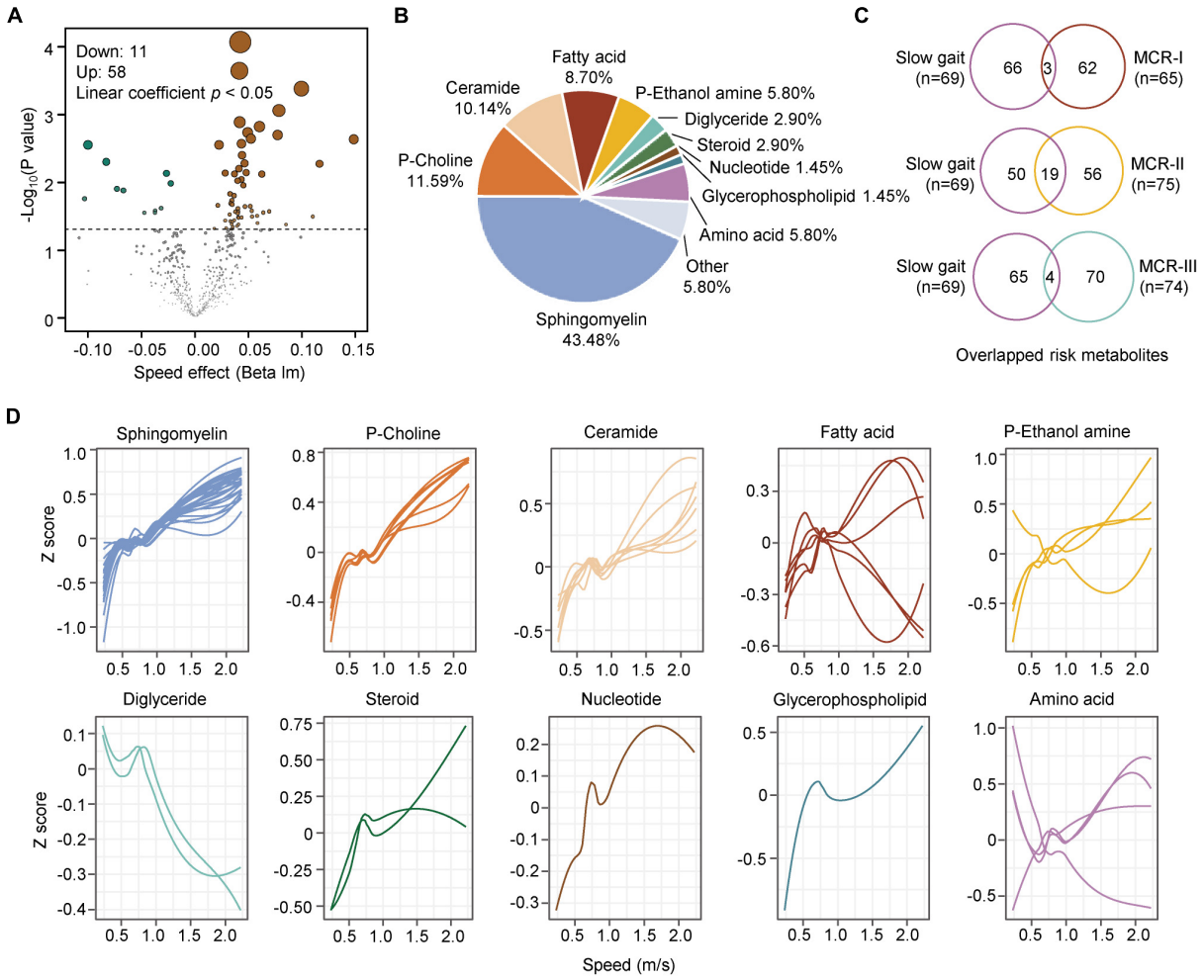

FIGURE 5
Metabolic characteristics associated with slow gait. **(A)** The volcano map shows the metabolites associated with slow gait (linear coefficient, $p < 0.05$). **(B)** Classification of the significantly changed metabolites with step speed. **(C)** Overlap analysis of metabolites associated with slow gait and those associated with MCR-I, MCR-II, and MCR-III (logistic regression, $p < 0.05$). **(D)** The correlations between slow gait and 10 classes of gait speed-associated metabolites are plotted with a Loess curve.

MCR investigation, which suggests the application of these approaches to reveal the pathobiological mechanism of MCR. Metabolomic investigations provided a number of clues in identifying specific amino acids and lipids for the prediction of cognitive decline (Li et al., 2019; Semba et al., 2020). Additionally, early identification of the subpopulation of MCR with the tendency of developing cognitive impairment, dementia, or AD provides opportunities to give timely preventive strategies (Verghese, 2021). Notably, MCR shares connections but also has synergistic discrepancies with other cognitive impairment syndromes, such as MCI, and the causal-effective association between them remains to be elucidated (Semba et al., 2020; Cheng et al., 2021). To exclusively focus on MCR-only individuals, we rationally divided the population into four groups, Neither, MCR-only, CI-only, and MCR-CI, and this grouping method was verified by disparities in both clinical and metabolic characteristics (**Figures 1**, **2**).

Targeting MCR-only participants, we verified the plasma metabolome and lipidome of MCR based on a large multi-center cohort study in China. First, MCR was classified into three distinct metabolic subtypes: MCR-I, MCR-II and MCR-III. Those individuals with the MCR-III subtype were more likely to develop CI than the others, followed by MCR-II and MCR-I. As the present results indicated that MCR-III was the most striking metabolic subtype among the three, we further explored the predictive models and determined the best-performing one with a model AUROC above 0.9, showing a good predictive performance (**Figures 4B,C**). More precisely, the model was composed of the six metabolites which were used as key markers to distinguish MCR-III from other MCRs. Thus, we assumed

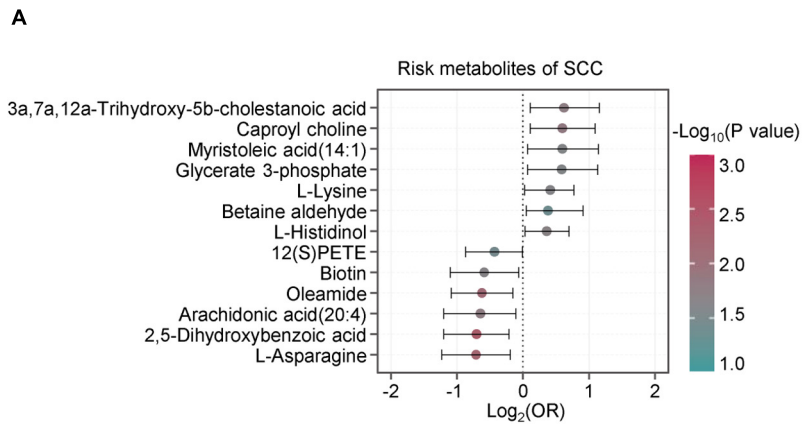

FIGURE 6
Metabolic characteristics associated with subjective cognition complaints. **(A)** The forest figure shows the metabolites associated with cognitive complaints (logistic regression, $p < 0.05$). The metabolites are ranked by the crude odds ratios (OR). The segment of each metabolite means 95% CI. **(B)** Overlap analysis of metabolites associated with complaints and those associated with MCR-I, MCR-II, and MCR-III (logistic regression, $p < 0.05$).

that the present findings supported the reasonable stratification of MCR.

Regarding the metabolic and lipidomic characteristics of the two components of MCR, overlapping result discovered that a larger number of common risk metabolites between SCCs and MCR-III, while the SCCs people patients tend to develop cognitive impairment (Semba et al., 2020). A previous multi-center study showed that SCCs rather than SG contributes more to the progression of dementia after the diagnosis of MCR (Verghese et al., 2019). The metabolic alterations of SCCs and SG justified our stratification of MCR and strengthened the previous assumption that MCR-III was mostly related to cognitive deterioration.

To our knowledge, our findings are the first to provide an overview of the metabolic and lipidomic profile of the pure MCR population and favor previous verification that plasma metabolites are associated with cognitive aging and cognitive decline (Ackerman et al., 2018; Bernath et al., 2020; Lefèvre-Arbogast et al., 2021). Triglycerides are significant in maintaining the homeostasis of specific fatty acids. When triglycerides are disrupted by inner and outer damaging stimulators, toxic saturated lipids accumulate, causing overproduction of toxic acyl-carnitines, and saturated ceramides, and activation of the NF-κB pathway (Ackerman et al., 2018). Specifically, the level of long-chain polyunsaturated triglycerides significantly reduced in the precursor stage of MCI and dementia (Bernath et al., 2020). In this study, triglycerides with saturated side chains increased in the MCR-III subtype, while the triglycerides with unsaturated side chains manifested the opposite changes.

Disorders of plasma phospholipids were reported in predicting antecedent cognitive impairment in older adults (Mapstone et al., 2014; Toledo et al., 2017). Phosphatidylcholine (PC) is an important class of lipids for cognitive health. Reduced PC species, such as PC(33:2), PC(34:2), PC(35:2), PC(36:2), PC(37:2), and PC(34:3), showed the association with the loss of cognitive function (Shea, 2019). A group of 10 plasma lipids were identified, and the level of PCs and acylcarnitine significantly reduced in participants who developed amnesic MCI or AD within a 2 to 3-year time frame (Mapstone et al., 2014). A longitudinal study found that PC(16:0_18:2), PC(18:0_18:1), and PC(18:1_18:1) were positively correlated with the performance of global and specific cognitive domains. Among cognitively unimpaired older individuals, PC (14:0_14:0) was independently associated with slower cortical thinning and amyloid deposition (Li et al., 2019). MCR is a pre-dementia syndrome, pathologically with lower overall cortical thickness and regional gray matter volume (Beauchet et al., 2016; Blumen et al., 2017). In our study, a low level of PC(40:3) is a striking feature to identify the MCR-III subtype. Additionally, PC(40:3) was one of the six key metabolites in the prediction model to distinguish MCR-III from other MCRs.

In addition, our results shared concordance with previous findings. For example, B vitamins slow the course of cognitive decline (Smith et al., 2018). Palmitoleic acid, myristoleic acid, and alpha-linolenic acid were all reported to be closely correlated with cognition (Varma et al., 2018; Wang et al., 2020). Compared with the control group, the serum level of linoleic acid, myristic acid, and palmitic acid decreased in MCI and AD patients.

However, there are still some limitations to this study. The main body of our metabolic and lipidomic findings was from one-time collected biological samples based on

an ongoing longitudinal multi-center cohort; therefore, we accessed limited causal-effective evidence. In addition, because the number of MCRs was not large enough, most of the MCR-related metabolites were not significant when multiple testing correction using False Discovery Rate (FDR) was carried out. Therefore, most of our tests used raw *p*-values. Although the analysis of metabolic and lipidomic data adjusted some covariables, the comorbidities in the data analysis such as sleep disorders and depressive and diabetes mellitus, would benefit future investigations.

Motoric cognitive risk syndrome in the pre-dementia phase has distinct metabolic subtypes, and SCC and SG display discordant metabolic features in developing MCR. The pathogenesis and mechanism of MCR need further investigations.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Committee of West China Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XS, WL, QX, LD, and BrD: conception and design of the study. XS, YLi, MG, YLu, LZ, XlL, XhL, BD, JY, and QX: acquisition and analysis of data. WL, XS, LD, and BrD: drafting a significant portion of the manuscript and figures. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Key R&D Program of China (Nos. 2018YFC2000305 and 2018YFC2002400); the Project of Max Cynader Academy of Brain Workstation, WCHSCU (No. HXYS19005); the Department of Aging and Health, National Health Commission PRC (No. ZX2019023); and the Chengdu Science and Technology Bureau Major Science and Technology Application Demonstration Project (No. 2019YF0900083SN). The financial sponsors had no role in the design, implementation, analyses, or reporting of the results.

Acknowledgments

We thank all the volunteers for their participation and personnel for their contribution to the WCHAT study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.977191/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Mini Review
PUBLISHED 23 September 2022
DOI 10.3389/fnagi.2022.1002096

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 24 July 2022
ACCEPTED 05 September 2022
PUBLISHED 23 September 2022

CITATION
McDonough IM, Nolin SA and Visscher KM (2022) 25 years of neurocognitive aging theories: What have we learned?
Front. Aging Neurosci. 14:1002096.
doi: 10.3389/fnagi.2022.1002096

25 years of neurocognitive aging theories: What have we learned?

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The past 25 years have provided a rich discovery of at least four fundamental patterns that represent structural and functional brain aging across multiple cognitive domains. Of the many potential patterns of brain aging, few are ever examined simultaneously in a given study, leading one to question their mutual exclusivity. Moreover, more studies are emerging that note failures to replicate some brain aging patterns, thereby questioning the universality and prevalence of these patterns. Although some attempts have been made to create unifying theories incorporating many of these age-related brain patterns, we propose that the field's understanding of the aging brain has been hindered due to a large number of influential models with little crosstalk between them. We briefly review these brain patterns, the influential domain-general theories of neurocognitive aging that attempt to explain them, and provide examples of recent challenges to these theories. Lastly, we elaborate on improvements that can be made to lead the field to more comprehensive and robust models of neurocognitive aging.

KEYWORDS

neurocognition, fMRI, aging, older adults, theory, review, maintenance, compensation

Introduction

Understanding human brain aging became much more feasible following the advent of non-invasive-neuroimaging methods. The following 25 years yielded many observed patterns of brain aging and many neurocognitive theories of aging proposed to explain those patterns. In this review, we summarize early theories that explained domain-general declines in cognition and more recent patterns of brain aging that have been subsequently observed (**Figure 1** and **Table 1**). These patterns have been used as evidence toward various modern neurocognitive aging theories. We provide examples of recent challenges to the generalizability of previously observed patterns, implicating

a need for more robust theories. We then discuss ways to build on these inconsistencies to advance theories of neurocognitive aging.

For clarity, we distinguish between "brain aging patterns" and "neurocognitive aging theories" such that multiple theories may explain a brain aging pattern (i.e., observed phenomenon) and some brain aging patterns may not have an explicit theory tied to them but may have theoretical mechanisms suggested when first described. We refer to theories as an overarching framework that goes beyond the observed phenomenon and provides mechanisms, related constructs, and predictions for a brain aging pattern. *Italics* are used when describing theories to differentiate theoretical inferences from observed data.

Early neurocognitive aging theories

Building upon notions of cognitive-brain deficits from neuropsychological and lesion approaches, one early neurocognitive theory of aging based on structural magnetic resonance imaging (MRI) was the *Frontal Lobe Hypothesis of Aging*. This hypothesis emphasized early shrinkage of the prefrontal cortex (PFC) in middle-age purportedly responsible for multiple cognitive deficits (e.g., West, 1996) and was concordant with white matter disconnection theories to explain generalized cognitive slowing with age (Cerella, 1990; Salthouse, 1992). Relatedly, the *Last-In-First-Out Hypothesis* proposed that the last brain regions to myelinate were the most vulnerable to degradation, pointing again to the PFC because of its early white matter degradation (Reisberg et al., 1999).

Early functional neuroimaging techniques ($Xenon^{133}$ inhalation or positron emission tomography, PET) showed consistency with structural MRI scans, evidencing either stable or declining patterns of cerebral blood flow in older age (West, 1996). These patterns of functional under-recruitment often were attributed to a decline in neural resources (e.g., Logan et al., 2002). However, a few PET studies suggested a pattern of age-related *hyper*activity in the PFC and sensory cortex (e.g., Grady et al., 1992; Cabeza et al., 1997). Subsequent studies, including those using functional MRI (fMRI), continued to show mixed patterns of increases and decreases in brain activity during various cognitive tasks that were not easily explained by early structural theories.

Influential patterns of brain aging

Loss of neural distinctiveness/differentiation

Dedifferentiation refers to the process of becoming less distinct. A neural dedifferentiation/distinctiveness pattern refers to brain activity becoming less selective and discretely organized with age (Koen and Rugg, 2019). For example, brain regions that selectively activate in response to a specific stimulus, such as the ventral visual cortex for visual objects and faces, do not activate as selectively in older adults (Park et al., 2004). Dedifferentiation has been proposed to be caused by declines in the brain's primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Lalwani et al., 2019; Chamberlain et al., 2021) and the loss of dopamine receptors in PFC and striatal regions that help regulate attention to specific details (e.g., Li et al., 2001).

This pattern also has been extended to the declines in differentiation of brain networks (Chan et al., 2014; Cassady et al., 2020; Pedersen et al., 2021). In young adults, brain networks show distinct patterns of synchronous temporal fluctuations. Portions of these networks also are recruited when engaged in a task but are less distinguishable in older adults (Grady et al., 2016). These declines in differentiation (or desegregation) are associated with poorer cognition both in cross-sectional (Park et al., 2010; Goh, 2011) and longitudinal studies (Ng et al., 2016; Malagurski et al., 2020).

Brain maintenance

Brain maintenance encompasses many of the patterns of brain degradation into a unified theme (Nyberg et al., 2012). Brain maintenance emphasizes that not all older adults exhibit the same patterns of aging; some show an absence of typical age-related patterns, representing "preserved" brain structure and function from young adulthood. Similarly, the *Scaffolding Theory of Aging and Cognition* (STAC) proposed that chronological age is not the driver of brain alterations throughout the lifespan (Park and Reuter-Lorenz, 2009). Rather, neural insults (e.g., brain shrinkage, dopamine depletion, white matter degradation) could occur at any age and these neural insults cause alterations in brain functioning. The revised theory (*STAC-r*) incorporates life-course experiences more explicitly (e.g., stress, fitness, education) that affect brain degradation or preservation (Reuter-Lorenz and Park, 2014). Thus, a middle-aged adult with many negative life-course experiences might have a brain resembling a typical older adult. Brain aging patterns that deviate from a maintained or youthlike state often are related to poorer cognition.

Neural compensation due to brain degradation

In contrast to deficit perspectives of aging, a neural compensation pattern is when aging is related to increases in neural activity, particularly in the PFC, thought to benefit cognition. Such age-related increases have been observed in bilateral PFC activity during demanding tasks (e.g., Cabeza, 2002; Reuter-Lorenz and Cappell, 2008), in the PFC

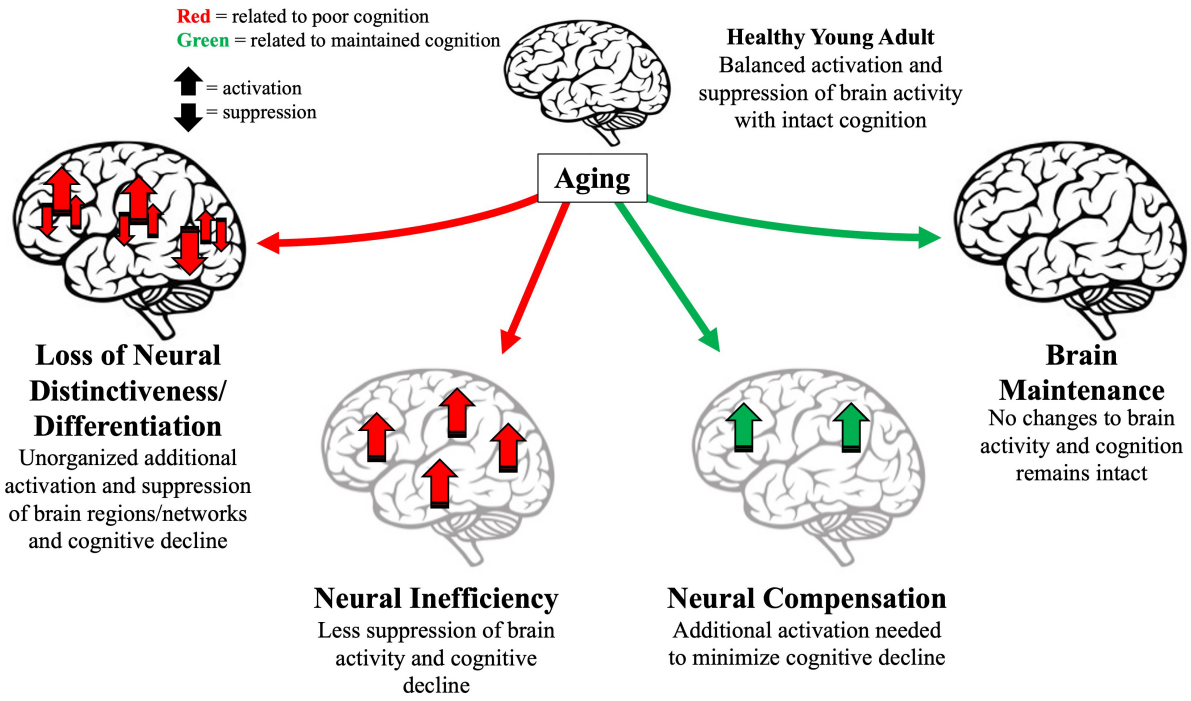

FIGURE 1
Illustration of four major patterns associated with older age. Arrows represent activation or suppression of brain activity associated with maintained (green) or poor (red) cognitive performance. Light gray brains represent brain structure degradation. Location of arrows represent primary brain areas patterns implicated in brain patterns. Loss of neural distinctiveness/differentiation **(left)** is characterized by decreased difference of brain signals to different perceived categories or loss of modularity of specific brain networks. Neural inefficiency **(lower left)** is characterized by non-beneficial increases in brain activity. Neural compensation **(lower right)** is characterized by beneficial increases in frontoparietal regions. Brain maintenance **(right)** is characterized by some older adults' brain structure and function as in young adulthood **(top)**.

TABLE 1 Summary of key aspects of the four major brain aging patterns.

	Loss of neural distinctiveness /Differentiation	Brain maintenance	Neural compensation	Neural inefficiency
Relation with PFC/PPC	Decreased network segregation in frontal networks	Youthlike or longitudinally maintained levels of structure and function	Increases in brain activity and connectivity; decreases in brain structure	Increases in brain activity
Relation with other brain regions	Decreased network segregation in non-frontal networks; Loss of brain signal selectivity in sensory and motor cortices	Youthlike or longitudinally maintained levels of structure and function	Increases in activity in new/secondary brain regions	Increases in brain activity
Relation with cognition	Lower distinctiveness/differentiation is associated with lower cognition	The more youthlike or maintained longitudinally maintained, the better cognition	Increases in brain activity in PFC/PPC associated with better cognition	Increases in brain activity is not related to cognition or is related to lower cognition
Mechanisms	Loss of dopaminergic neurons, loss of GABAergic neurons	Loss of neurotransmitter systems; elevated neuropathological lesions; genetic variants; lifestyle factors; environmental factors	Decreases in brain activity (e.g., sensory cortex, medial temporal lobe, default mode regions); decreases in brain structure; elevated neuropathological lesions; genetic variants; lifestyle factors; environmental factors	Loss of GABAergic neurons; lower white matter integrity
Key theories/articles	Li et al., 2001; Reuter-Lorenz and Park, 2014;Koen and Rugg, 2019	Nyberg et al., 2012; Reuter-Lorenz and Park, 2014	Greenwood, 2007; Davis et al., 2008; Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz and Park, 2014; Cabeza et al., 2018; Spreng and Turner, 2019	Reuter-Lorenz et al., 2001; Logan et al., 2002

with lower brain activity in sensory cortex (*Posterior-to-Anterior Shift in Aging* or *PASA*; Davis et al., 2008), in the PFC and the medial temporal lobes (MTL) with decreases in nearby white matter (Daselaar et al., 2015), and in the coupling of PFC regions with the MTL (Daselaar et al., 2006; Dennis et al., 2008) or default mode regions; Spreng and Turner, 2019). Given the connectivity between the PFC and the lateral parietal cortex (Dosenbach et al., 2008; Vincent et al., 2008), such compensatory increases have been extended to the parietal lobe (e.g., Nagel et al., 2009; Huang et al., 2012).

The observed increases in frontoparietal activity have been considered a direct response to age-related structural or functional degradations in the PFC, MTL, posterior/sensory cortex, or an inability to modulate the default mode network (e.g., Li et al., 2001; Greenwood, 2007; Davis et al., 2008; Park and Reuter-Lorenz, 2009; Spreng and Turner, 2019). This compensatory neural response should minimize the impact of brain degradation on cognition, which we dubbed the *Atrophy-Compensation Hypothesis* (McDonough and Madan, 2021). This neural compensation should occur in nearby or contralateral brain regions to the sites of brain atrophy (e.g., Cabeza et al., 2002; Greenwood, 2007; Reuter-Lorenz and Cappell, 2008). In *STAC*, neural compensation was termed scaffolding and referred to the activation of secondary brain regions/networks (primarily in the PFC) that differed from the original (young) brain regions used to engage in a task (Park and Reuter-Lorenz, 2009). Scaffolding is similar to cognitive reserve in the context of cognitive reserve (Stern, 2002). Recently, the idea of neural compensation has been refined into different forms depending on when and where in the brain they occur (Cabeza et al., 2018). Regardless of the different forms, each generally supports cognition.

Neural inefficiency

Brain activity increases also could be due to an inefficient neural system that either does not contribute to current cognitive processes (non-selective activity) or is detrimental to ongoing processes (Reuter-Lorenz et al., 2001; Logan et al., 2002). A neural inefficiency pattern is when an increase in brain activity relates to poorer cognition with aging. Such activity increases might stem from deficits in inhibitory neural circuitry (Lalwani et al., 2019) or lower white matter integrity (Bennett and Rypma, 2013). Accordingly, some brain regions do not show increased activity because they are actively suppressed in young adults, but when the "brakes" are released, increases in brain activity can be revealed. This perspective also predicts that negative relationships exist between white matter integrity and brain activity in older adults because the failures to inhibit brain activity might stem from white matter disconnections (Bennett and Rypma, 2013). Some support for neural inefficiency comes from studies showing that cognitive training decreases brain activity (Lustig et al., 2009; McDonough et al., 2015; Nguyen et al., 2019; Ross et al., 2019).

Challenges to neurocognitive theories of aging

¿Qué pasa con PASA?

Morcom and Henson (2018) sought to replicate a neural compensation pattern predicted by *PASA* in a large adult lifespan sample across two different cognitive tasks. Using a model-based decoding approach, they also tested whether the predicted age-related increases in PFC (*via* a multivariate pattern) carried additional information about cognitive performance. Although older age was associated with increases in PFC activity in both tasks, concomitant age-related decreases in sensory cortex were not found, failing to support *PASA*. In fact, the visual-perception task showed age-related increases in brain activity in sensory cortex. Moreover, the patterns of PFC activity carried less information about cognitive performance as age increased, did not predict cognitive performance beyond that found in the sensory cortex, and revealed strong evidence in favor of the null hypothesis using Bayes factor scores. Thus, this study failed to find evidence for *PASA* or evidence for compensation in the PFC but was consistent with a pattern of neural inefficiency.

Revisiting the atrophy-compensation hypothesis

Given the proposal that brain degradation should be associated with increased brain activity (regardless of whether it is compensatory), supporting evidence is surprisingly sparse in healthy aging samples (Brassen et al., 2009; Pudas et al., 2013). Using a sensitive marker of brain degradation (fractal dimensionality), McDonough and Madan (2021) directly tested whether brain degradation in one hemisphere was associated with increases in PFC activity in nearby or contralateral brain regions during successful memory encoding and retrieval. Bayes factor scores revealed moderate to strong evidence across PFC regions supporting no relationship between brain degradation and brain activity in either task in the PFC, challenging the *Atrophy-Compensation Hypothesis*.

Toward better neurocognitive aging theories

These counter examples suggest that some neurocognitive aging theories need revising if the fundamental patterns of

data on which they are partly based are unreliable. More theoretical progress might be made if changes are made in (a) how theory testing (or lack thereof) is conducted and (b) how analyses are conducted to reveal brain patterns, especially if drawing from heterogeneous samples. Both changes have important implications for the inferences that can be made from brain patterns.

The impact of pre-registration

We currently do not have a good grasp as to the exclusivity or co-existence of the four major patterns of brain aging outlined here. Better adjudication between neurocognitive aging theories could shed light onto how these patterns relate to one another or represent distinct facets of the aging process. However, most findings from individual neurocognitive aging studies either support one of the many existing patterns of brain aging or were not designed to test major theories of neurocognitive aging. Furthermore, most brain studies on aging have (understandably) not been pre-registered. Without pre-registrations, we do not know which theories originally guided a study, whether the original hypotheses were abandoned after viewing the results, or whether results were interpreted within existing theories *post-hoc*. For example, one might design a study to investigate age-related bilateral PFC activity but if that pattern was not found, then the framing might shift to one consistent with brain maintenance. These practices are akin to a theoretical "file drawer" effect in which some theories continue to be critically unexamined, and no clear consensus exists for a leading theory of neurocognitive aging. Thus, one first step is to document what brain aging pattern is predicted as guided by a theory in a pre-registration. Doing so will help establish the ease (or difficulty) of finding a given brain aging pattern as relevant to a new experimental design and context.

Testing competing models

One also could explicitly test competing predictions between different neurocognitive theories of aging. Indeed, some theories make predictions that are either mutually exclusive or somewhat incompatible. For example, the *Atrophy-Compensation Hypothesis* predicts an inverse relationship between structural integrity and functional activation (McDonough and Madan, 2021). Theories with this hypothesis as a component might predict that if structural decline occurs in sensory cortex, then brain activity should increase in nearby or contralateral brain regions. While structural declines do occur in posterior regions (Salat et al., 2004; Fjell et al., 2009; Storsve et al., 2014), other theories (e.g., *PASA*) or hypotheses derived from other brain patterns (e.g., neural dedifferentiation) propose decreases in posterior brain activity, which would lead to positive rather negative associations. Similarly, one also could test which of multiple mechanisms best explains age-related increases in PFC activity: PFC structural degradation in the opposite hemisphere, lower posterior brain activity, or neural dedifferentiation. By engaging in model comparisons or designing paradigms to test competing accounts, the field can move beyond providing support for an existing theory and start ruling out or modifying existing theories that do not explain patterns of brain aging as well as others (Popper, 1963).

Bridging seemingly different brain patterns

These analytic strategies may not be appropriate if multiple patterns of brain aging are due to the same underlying cause or are different manifestations of the same theory. For example, lower sensory cortex activity might be one manifestation of neural dedifferentiation in sensory cortex. Both decreased brain activity and neural dedifferentiation in sensory cortex might be caused by underlying degradations of white matter in nearby tracts (Rieck et al., 2020). Similarly, network desegregation might simply be a different method of testing neural dedifferentiation. Indeed, both network desegregation and neural dedifferentiation are significantly correlated (albeit weakly) with one another (Cassady et al., 2020). A third factor might cause both patterns independently or one pattern may cause the other. One candidate is the loss of inhibition, which has also been linked to neural inefficiency. However, more critical tests are needed either linking or dissociating these patterns into current neurocognitive theories.

Multiple brain aging patterns in different groups of older adults

In the previous sections, we assumed that older adults (as a whole) exhibited homogeneous patterns of brain aging in a given sample. However, some brain aging patterns might be found in only subsets of aging adults, and thus can be better understood through individual differences. As documented in *STAC*, older adults who are more physically fit, engage in more cognitive stimulation, or have fewer genetic risk factors have been proposed to employ neural scaffolds more effectively (Park and Reuter-Lorenz, 2009). Relatedly, brain maintenance acknowledges that variability in genetic and lifestyle factors help explain why some older adults can maintain a healthy (youthlike) brain (Nyberg et al., 2012). A recent study provides an illustration of how one might explore multiple brain aging patterns among subgroups of older adults. Chen et al. (2022) first separated middle-aged and older adults into "successful" and "average" cognitive agers using longitudinal changes in cognition. Successful cognitive agers

exhibited similar levels of brain activity as young adults in sensory cortex using a subsequent-memory contrast, supporting the brain maintenance pattern. In contrast, the average agers showed reduced subsequent-memory activation compared to both young adults and successful agers in both PFC and sensory cortex. This perspective emphasizes that different people can show different patterns of brain aging. While we acknowledge that many studies have successfully shown individual differences, the direction and location of brain activation often are difficult to predict and such predictions have not been made concrete in many neurocognitive aging theories.

Multiple brain aging patterns in the same brain

A more overlooked and conceptually distinct idea is that multiple patterns of brain aging might coexist in each person (e.g., Logan et al., 2002; Cassady et al., 2020). For example, an individual might exhibit a loss of differentiation in one part of the brain (e.g., visual cortex) and exhibit brain maintenance in a different part of the brain (e.g., the PFC). In this case, a person exhibits at least two brain aging patterns. However, we do not often characterize people at the individual level. Large, diverse samples and person-centered clustering methods might be a practical approach that can characterize common brain patterns in subgroups. The study by Chen et al. (2022) continues to be illustrative. Not only did successful agers exhibit a "maintained brain" in sensory cortex, but they also showed greater subsequent-memory activation in the PFC than both average cognitive agers and young adults, consistent with a neural compensation pattern. If we tentatively assume that the successful aging group was a homogeneous subgroup, then inspecting each person's brain activity should show two patterns (brain maintenance and neural compensation) but in different regions of the brain.

Theories need to prospectively predict aging brain patterns

As elaborated by West (1996), a valuable theory of neurocognitive aging should be able to accurately predict (a) when age-related deficits should be observed, (b) when age-related differences are not observed (age-invariance), and (c) identify the specificity or generality of the sources of the effects. Although West (1996) was articulating the relationships between neuropsychological tests and brain integrity, the same holds for modern neurocognitive aging theories. How precisely can we predict which brain regions will show functional increases, decreases, or remain unchanged with age? Can we predict the mechanism of brain aging patterns? Could those predictions be made precisely enough to be pre-registered?

Recommendations for future research

- Use existing neurocognitive theories to inform directionally (i.e., increases vs. decreases) and regionally specific hypotheses.
- Pre-register theories and hypotheses motivating the study.
- Create analyses that test competing or alternative models or mechanisms.
- Use sufficiently large and diverse sample sizes to test for heterogenous patterns of brain aging.

Conclusion

The last 25 years of cognitive aging research has resulted in a rich body of aging brain patterns and multiple neurocognitive aging theories. However, understanding of the aging brain has been hindered due to little crosstalk between those theories. Recently, even the underlying brain patterns that gave rise to some of those theories have been questioned, providing an impetus to critically inspect existing neurocognitive aging theories. By better understanding (a) which aspects of theories overlap with one another, (b) which aspects of a given theory survive direct tests, and (c) the conditions under which some brain patterns might occur, existing theories can be falsified (or modified), leading to more comprehensive and robust models of neurocognitive aging that make generalizable predictions about the aging brain.

Author contributions

IM: conceptualization, visualization, writing – original draft preparation, and writing – review and editing. SN and KV: visualization, writing – original draft preparation, and writing – review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 29 September 2022
DOI 10.3389/fnagi.2022.972480

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 18 June 2022
ACCEPTED 26 August 2022
PUBLISHED 29 September 2022

CITATION
Huang K-L, Chang T-Y, Wu Y-M, Chang Y-J, Wu H-C, Liu C-H, Lee T-H and Ho M-Y (2022) Mediating roles of leukoaraiosis and infarcts in the effects of unilateral carotid artery stenosis on cognition. *Front. Aging Neurosci.* 14:972480. doi: 10.3389/fnagi.2022.972480

Mediating roles of leukoaraiosis and infarcts in the effects of unilateral carotid artery stenosis on cognition

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Background and objectives: Leukoaraiosis and infarcts are common in patients with carotid artery stenosis (CAS), and CAS severity, leukoaraiosis and infarcts all have been implicated in cognitive impairments. CAS severity was not only hypothesized to directly impede specific cognitive domains, but also transmit its effects indirectly to cognitive function through ipsilateral infarcts as well as periventricular leukoaraiosis (PVL) and deep white matter leukoaraiosis (DWML). We aimed to delineate the contributions of leukoaraiosis, infarcts and CAS to different specific cognitive domains.

Materials and methods: One hundred and sixty one participants with unilateral CAS (>50%) on the left (n = 85) or right (n = 76) side and 65 volunteers without significant CAS (<50%) were recruited. The PVL, DWML, and infarct severity were visually rated on MRI. A comprehensive cognitive battery was administered and standardized based on age norms. Correlation and mediation analyses were adopted to examine the direct and indirect influence of CAS, leukoaraiosis, and infarct on specific cognitive domains with adjustment for education, hypertension, diabetes mellitus, and hyperlipidemia.

Results: Carotid artery stenosis severity was associated with ipsilateral leukoaraiosis and infarct. Left CAS had direct effects on most cognitive domains, except for visual memory and constructional ability, and transmitted its indirect effects on all cognitive domains through ipsilateral PVL, and on constructional ability and psychomotor through infarcts. Right CAS only had negative direct effects on visual memory, psychomotor, design fluency and color processing speed, and transmitted its indirect effects on visual memory, word and color processing speed through ipsilateral infarcts.

The trends of direct and indirect cognitive effects remained similar after covariate adjustment.

Conclusion: Left and right CAS would predominantly lead to verbal and non-verbal cognitive impairment respectively, and such effects could be mediated through CAS-related leukoaraiosis and infarct. Given that cognition is subject to heterogeneous pathologies, the exact relationships between markers of large and small vessel diseases and their composite prognostic effects on cognition requires further investigation.

KEYWORDS

cognition, carotid artery stenosis (CAS), leukoaraiosis (LA), infarct, mediation analysis, white matter hyperintensities

Introduction

Carotid artery stenosis (CAS) is one of the major risk factors for stroke (Howard et al., 2021), and it can also lead to remarkable cognitive impairments even in patients with asymptomatic CAS (Chang et al., 2013). The neurocognitive changes in CAS patients are usually attributed to large vessel disease (LVD)-related chronic cerebral hypoperfusion and thrombotic emboli (Wallin et al., 2018). The direct associations between cerebral hypoperfusion and cognitive impairments in patients with CAS have been demonstrated by different imaging markers, including Doppler-based breath holding index (Balestrini et al., 2013), arterial spin labeling (Schröder et al., 2019) from MRI perfusion, and disrupted neural connectivity on functional MRI (Chang et al., 2016; Huang et al., 2018). Furthermore, left and right CAS are more related to verbal and non-verbal cognitive impairment as the lateralization effect (Huang et al., 2017). However, whether restoration of cerebral perfusion by carotid revascularization procedure is beneficial to cognition is inconclusive (Plessers et al., 2014).

On the other hand, leukoaraiosis and lacunar infarcts are manifestations of small vessel disease (SVD), and they have also been commonly observed in patients with CAS (Kandiah et al., 2014; Pini et al., 2020). Furthermore, the extent of leukoaraiosis is associated with CAS severity (Saba et al., 2009). Irrespective of their pathogeneses, leukoaraiosis (Appelman et al., 2010; Chowdhury et al., 2011) and infarcts (Saczynski et al., 2009) alone can independently contribute to cognitive impairments in individuals with advancing ages and various kinds of neurological conditions (Gorelick et al., 2011; Chui and Ramirez Gomez, 2017). As the origins of neurocognitive changes in CAS patients are multifactorial and inter-related, it is intrinsically complicated to investigate the relationship between cerebrovascular markers and cognition in CAS patients.

In literature, most studies investigating cognitive functions in patients with CAS have been based on group comparison designs to demonstrate cognitive sequalae from certain pathologies, but such approaches may not convey enough information regarding how CAS exerts its effect on cognition through the underlying LVD and SVD pathologies (Chang et al., 2013; Lal et al., 2017; Ihle-Hansen et al., 2021; Paraskevas et al., 2021). We reckoned to delineate these underlying pathologies on specific cognitive domains may have important implications for evaluating the treatment outcomes in patients with CAS. In this study, we proposed exploring the possible mediating roles of leukoaraiosis and infarcts in the associations between CAS and cognition might help to clarify these issues.

Materials and methods

Participants

A total of 161 participants with CAS (147 males, 14 females) attended for the outpatient clinics at the Department of Neurology, Linkou Chang Gung Memorial Hospital participated in this study. Their mean age was 65.7 years (SD = 8.5), ranging from 40 to 86 years old. They were recruited based on the following inclusion criteria, (a) unilateral internal carotid artery stenosis (either the left or right side of CAS $>$ 50%); (b) the score of the Mini Mental State Examination (MMSE) $\geq$ 20; (c) the score for the Clinical Dementia Rating Scale (CDR) $<$ 1; (d) right-hand dominance; (e) the scores on the National Institutes of Health Stroke Scale (NIHSS) $\leq$ 8; (f) the score for the Barthel Index $\geq$ 80; (g) the score for the Modified Rankin Scale $\leq$ 3. The exclusion criteria were: (a) stroke within the past 3 months at recruitment; (b) a history of psychiatric illness; (c) undergoing the coronary or peripheral arterial surgeries in the past 30 days at recruitment; (d) a history of traumatic head injury; (e) persistent moderate to severe dysphasia, which was defined as a score of $>$ 1 point of the

language item of NIHSS. According to the severity of left or right internal carotid artery stenosis, these participants were allocated to the left group ($n = 85$, stenosis of the left carotid artery > 50% and the right carotid artery < 50%), the right group ($n = 76$, stenosis of the left carotid artery < 50% and the right carotid artery > 50%).

In addition, 65 age- and gender-matched volunteers (54 males, 11 females) with stenosis of the left and right carotid arteries < 50% were recruited as the non-CAS group by advertisements placed around the hospital. Their mean age was 64.5 years (SD = 6.3), ranging from 54 to 81 years old. The inclusion criteria were as follows: (a) no history of neuropsychiatric disorders or head injuries; (b) the internal carotid artery stenosis on both sides were less than 50%. The reasons for including participants with no or milder CAS in this study were to substantiate the notion that cognitive impairments can be produced by severe CAS, and to increase the range of the grade of CAS as the predictor in mediation analyses.

The study protocol and procedure for obtaining informed consent were complied with the Helsinki Declaration and were approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 201601092B0, 103-7584A, and 201601675A0). All participants signed the written informed consent.

Imaging investigations

The grade of CAS in clinical participants was determined by digital subtraction angiography (DSA) according to the criteria proposed by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators (North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett et al., 1991). The grade of CAS of control group was determined by brain magnetic resonance angiography or color-coded carotid duplex if the DSA was not available.

Brain MRI was performed within 1 month after enrollment for both CAS and non-CAS groups, and the method of MRI evaluation has been described in previous studies (Huang et al., 2018). In brief, anatomical MRI was obtained at a 1.5- or 3.0-Tesla scanner with 5-mm slice thickness and 0.5-mm inter-slice gap for all sequences, including axial T1-weighted, fluid-attenuated inversion recovery (FLAIR). The severity of infarcts and leukoaraiosis on each hemisphere was visually rated by two neurologists. The severity of infarcts in both hemispheres was converted into a four-point scale, rated as 0 = no lesion, 1 = one focal lesion (≥ 5 mm), 2 = more than one focal lesions, and 3 = confluent lesions (Lee et al., 2017). The severity of periventricular leukoaraiosis (PVL) and deep white matter leukoaraiosis (DWML) was assessed by Fazekas scale on FLAIR sequence (Fazekas et al., 1987). The severity of PVL was defined as 0 = absence, 1 = "caps or pencil-thin lining," 2 = smooth "halo," 3 = irregular leukoaraiosis extending into the deep white matter, whereas, the severity of DWML was defined as 0 = absence, 1 = punctuate foci, 2 = beginning confluence of foci, 3 = large confluent areas.

Cognitive tests

Raw scores

A battery of comprehensive cognitive tests was administered in this study. These tests were chosen because our previous studies have shown they were sensitive to the cognitive deficits in patients with carotid stenosis (Huang et al., 2018, 2022). The CDR and MMSE were administered for general cognitive function evaluation. A Taiwanese adaptation of the California Verbal Learning Test-2 (Delis et al., 2000) and the Brief Visual Memory Test-Revised (BVMT-R) (Benedict, 1997) were administered on all participants to test verbal and visual memory, respectively. The Position Discrimination (PD) and Number Location (NL) subtests of the Visual Objection and Spatial Perception Battery (VOSP) (Warrington and James, 1991) were administered for testing the visuospatial functions. The constructional ability was examined by the Benton 3-Dimensional Construction Praxis Test (B3DCP) (Benton et al., 1994). The Purdue Pegboard Test (Tiffin, 1968) was used to measure the psychomotor function for both hands. The Color Trail Test (D'Elia et al., 1996) and the Category Fluency Test and Design Fluency Test of the Delis-Kaplan Executive System (Delis et al., 2001) were used to tap the verbal and non-verbal aspects of the executive functions. The mean reaction times of computerized Stroop word/color interference tests were used as the measures of processing speed as described in our previous study (Huang et al., 2022). The interval between the imaging investigations and cognitive assessment was less than 1 month for each participant.

T-score transformation

As more than 20 neuropsychological measures were recorded, a scale-reduction procedure was applied to minimize the potential redundancy of multiple comparisons (Huang et al., 2022). All raw testing scores for each participant were transformed to T-score (Mean = 50, SD = 10) based on the local corresponding age norms. In addition, we adopted a data-driven approach to carry out a principal component analysis (PCA) on all individually derived T-scores from approximately 40% ($n = 94$) of randomly selected participants in this study to extract the latent components corresponding to each cognitive measure. Seven components were extracted from this dataset by Varimax rotation, which accounted for > 72% of the total variance. The factor loadings for the cognitive measures corresponding to these components are summarized in **Supplementary Table A**. The T-scores of the cognitive measures within each component were averaged to derive the mean T-score for each specific cognitive domain.

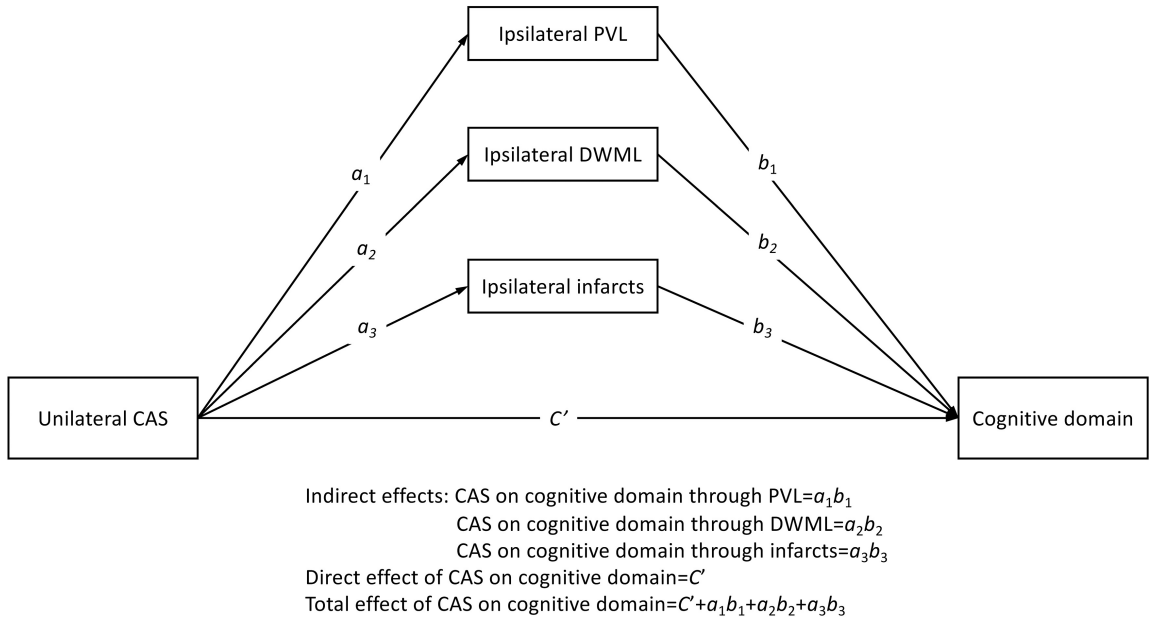

FIGURE 1
Conceptual parallel mediation model. Letters a_i are regression coefficients of the predictor variable in predicting three parallel mediators; and letters b_i and C_i' are the regression coefficients of mediators and predictors in predicting outcome variables, respectively (i = 1 to 3). The error term in each prediction is not shown. CAS, carotid artery stenosis; PVL, periventricular leukoaraiosis; DWML, deep white matter leukoaraiosis.

Data analysis

The demographic, clinical and cognitive data for each group were summarized by descriptive statistics. Depending on the scale of each measure, group comparisons were conducted by χ^2 tests or one-way analysis of variance (ANOVA) where appropriate. Bonferroni corrections were applied where appropriate for the *post hoc* comparisons between each group.

Mediation analyses

We adopted the PROCESS macro for SPSS Version 4 developed by Hayes (2022) to carry out a series of mediation analyses. As being shown in **Figure 1**, grade of unilateral CAS (%CAS) was used as the predictor variable for the direct effect evaluation, and the ipsilateral PVL, DWML and infarcts severity were the three parallel mediators for the indirect effect evaluation. The outcome variable was the mean T-score for each specific cognitive domain. We discretely examined the associations between CAS in either side (left vs. right) and each specific cognitive domain by utilizing a model template [PROCESS Model 4, Hayes (2022)]. Since the sampling indirect effects of CAS on specific cognitive domains were unlikely to be normally distributed, a large number of samples (n = 5000) of data were taken to derive the empirically generated 95% bootstrap intervals of the sampling distributions of the indirect effects (Hayes, 2022). In addition, years of education and vascular risk factors were used as covariates in the mediation analysis models to examine their effects on each cognitive domain. Statistical significance would be claimed when the direct, indirect or total effects (i.e., sum of direct and indirect effects) of unilateral CAS severity on each specific cognitive domain by the absence of zero within the confidence intervals.

Results

Demographic and clinical data

Table 1 shows the demographic and clinical data for all groups. The mean ages and gender ratios did not significantly differ between groups (ps $>$ 0.099). CAS patients had more prominent carotid stenosis severity and higher frequency of hypertension, hyperlipidemia, diabetic mellitus, coronary artery diseases and gouts than the non-CAS group, while the non-CAS group had higher education (ps $<$ 0.019). The difference or proportion of the above demographic and clinical conditions did not significantly differ between CAS groups. The CAS groups tended to present with higher leukoaraiosis and infarct severity than the non-CAS group and the frequency distributions of PVL, DWML, and infarct severity in the left and right cerebral hemispheres among groups were statistically significant (ps $<$ 0.05, see **Supplementary Table B**). In addition, the hemispheric PVL, DWML, and infarct severity tended to be

TABLE 1 Demographic and medical data for all groups.

	Group				
	Non-CAS	Left	Right		
M ± SD [95%CI]	***n* = 65**	***n* = 85**	***n* = 76**	***F***	***p***
Age, years	64.7 ± 6.3 [63.1, 66.3]	66.7 ± 8.3 [64.9, 68.5]	64.6 ± 8.5 [62.7, 66.6]	1.71	0.18
Education, years	11.2 ± 3.5 [10.3, 12.0]	9.0 ± 3.4 [8.3, 9.8]*	9.5 ± 3.8 [8.6, 10.4]*	6.87	0.001
Lt-CAS,%	10.1 ± 11.6 [7.2, 12.9]	80.1 ± 15.6 [76.7, 83.5]*	22.1 ± 18.3 [17.9, 26.8]*†	451.43	<0.001
Rt-CAS,%	8.0 ± 11.0 [5.3, 10.8]	21.0 ± 17.3 [17.3, 24.7]*	82.6 ± 14.0 [79.4, 85.8]*†	549.44	<0.001
***n* (%)**				χ^2	***p***
Male	54 (83)	80 (94)	67 (88)	4.64	0.099
Hypertension	21 (32)	63 (74)*	62 (82)*	42.59	<0.001
Hyperlipidemia	25 (39)	51 (60)*	54 (71)*	15.57	<0.001
Diabetic mellitus	7 (11)	26 (31)*	29 (38)*	13.88	<0.001
CAD	3 (5)	20 (24)*	21 (28)*	13.34	0.001
Gout	4 (6)	21 (25)*	18 (24)*	9.97	0.002

N = 226. CI, confidence interval; Lt, left; Rt, right; CAS, carotid artery stenosis; CAD, coronary artery disease; PVL, periventricular leukoaraiosis; DWML, deep white matter leukoaraiosis.
*$p < 0.05$ compared with the control group.
†$p < 0.05$ compared with the left group.

TABLE 2 Correlation between age, education, and vascular pathologies of the left and right sides.

	1	2	3	4	5	6	7	8	9	M	SD
1. Age, years	—									65.4	7.9
2. Edu, years	−0.30**	—								9.8	3.7
3. Lt-CAS,%	0.15*	−0.22**	—							40.5	34.8
4. Rt-CAS,%	−0.03	−0.12	−0.01	—						38.0	35.4
5. Lt-PVL[a]	0.31**	−0.32**	0.25**	0.16*	—					—	—
6. Rt-PVL[a]	0.30**	−0.23**	0.11	0.10	0.78**	—				—	—
7. Lt-DWML[a]	0.12	−0.10	0.21**	0.02	0.36**	0.37**	—			—	—
8. Rt-DWML[a]	0.14*	−0.13	0.05	0.22**	0.42**	0.49**	0.64**	—		—	—
9. Lt-infarct[a]	0.15*	−0.08	0.34**	0.10	0.28**	0.23**	0.39**	0.24**	—	—	—
10. Rt-infarct[a]	0.06	−0.15*	0.04	0.38**	0.30**	0.24**	0.17*	0.32**	0.36**	—	—

N = 226. CAS, carotid artery stenosis; DWML, deep white matter leukoaraiosis; Edu, education; Lt, left; PVL, periventricular leukoaraiosis; Rt, right.
[a]Based on Spearman ρ correlation analysis.
*$p < 0.05$; **$p < 0.01$.

more strongly correlated with the ipsilateral CAS severity than the contralateral CAS severity (Table 2).

Cognitive function comparisons

The mean (± SD) raw scores of the cognitive tests in this study are shown in Supplementary Table C. One-way ANOVA revealed that except for the NL subtest of the VOSP ($p = 0.064$), the effect of group was statistically significant on each measure (Fs > 3.59, ps < 0.03). *Post hoc* comparisons between groups indicated that the mean raw scores of nearly all cognitive measures for the left groups were significantly lower than those for the non-CAS group (ps < 0.05), except for the B3DCPT and VOSP scores. Likewise, most of the cognitive measures for the right group were also significantly inferior to those of the non-CAS group (ps < 0.05), but not the NL subtest of the VOSP. The differences in the mean raw scores of all cognitive measures between the two clinical groups were not significant (ps > 0.08).

Correlation and mediation analyses between cognition and vascular markers

The correlations of mean T-scores of specific cognitive domains with demographic data, CAS severity, leukoaraiosis and infarcts are demonstrated in Table 3. Overall, the verbal and visual memory, psychomotor function, design fluency and color processing speed were correlated with most of the vascular markers. However, the construction ability was not correlated with bilateral CAS severity, hypertension, hyperlipidemia or

TABLE 3 Correlation of cognition with demographic data and severity of carotid artery stenosis (CAS), leukoaraiosis, and infarct for the total sample.

	Verbal memory	Visual memory	Construction	Psychomotor	Design-FL	Word-PS	Color-PS
Edu, years	0.38**	0.38**	0.31**	0.18**	0.38**	0.32**	0.26**
Hypertension	−0.21**	−0.25**	−0.12	−0.29**	−0.22**	−0.27**	−0.26**
Hyperlipidemia	−0.18**	−0.05	−0.12	−0.15*	−0.16*	0.03	0.01
Diabetic mellitus	−0.11	−0.18**	−0.18**	−0.21**	−0.18**	−0.12	−0.13
Lt-CAS, %	−0.36**	−0.18**	−0.08	−0.24**	−0.24**	−0.37**	−0.31**
Rt-CAS, %	−0.17**	−0.29**	−0.11	−0.27**	−0.25**	−0.12	−0.28**
Lt-PVL[a]	−0.24**	−0.29**	−0.31**	−0.32**	−0.33**	−0.36**	−0.37**
Rt-PVL[a]	−0.18*	−0.21**	−0.24**	−0.26**	−0.25**	−0.25**	−0.30**
Lt-DWML[a]	−0.17*	−0.18**	−0.22**	−0.12	−0.22**	−0.11	−0.15*
Rt-DWML[a]	−0.14*	−0.22**	−0.23**	−0.21**	−0.24**	−0.15*	−0.22**
Lt-Infarct[a]	−0.24**	−0.21**	−0.22**	−0.25**	−0.25**	−0.21**	−0.25**
Rt-Infarct[a]	−0.20**	−0.26**	−0.10	−0.22**	−0.28**	−0.26**	−0.30**
M ± SD	45.59 ± 11.20	43.01 ± 11.43	46.00 ± 13.24	41.56 ± 10.88	45.37 ± 8.99	43.75 ± 13.42	41.17 ± 14.67

N = 226. CAS, carotid artery stenosis; Design-FL, design fluency; DWML, deep white matter leukoaraiosis; Edu, years of education; Lt, left; PS, processing speed; PVL, periventricular leukoaraiosis; Rt, right.
[a]Based on Spearman ρ correlation analysis.
*$p < 0.05$; **$p < 0.01$.

Rt-Infarct, neither was word processing speed correlated with Rt-CAS, hyperlipidemia, diabetes mellitus, or Lt-DWML.

Considering the inter-relations among CAS, leukoaraiosis, infarcts and cognition, mediation analyses were adopted to delineate the influence of each vascular component on cognitive domains. As shown in **Figure 2**, Lt-CAS positively predicted the ipsilateral PVL, DWML and infarcts severity (ps < 0.001), accounting for more than 10% (from 10.2 to 19.6%) of all variances in specific cognitive domains. Lt-CAS directly predicted most of the cognitive domains, except for visual memory and constructional ability, and its indirect effects on all cognitive domains through ipsilateral PVL, as well as on constructional ability and psychomotor domains through Lt-infarct, were significant. After adjusting for education, hypertension, hyperlipidemia and diabetes mellitus, some of the effects were diminished, including (1) Lt-CAS direct effects on psychomotor and design fluency, (2) Lt-PVL indirect effects on verbal and visual memory, and (3) Lt-infarct indirect effects on constructional and psychomotor domains (see **Table 4**).

Figure 3 shows Rt-CAS only positively predicted the severity of ipsilateral DWML and infarcts (ps < 0.001), respectively, but not ipsilateral PVL (p = 0.957), which accounted for more than 7% (from 7.7 to 18.2%) of all variances of the specific cognitive domains. As shown in **Table 4**, Rt-CAS directly predicted non-verbal domains, including visual memory, psychomotor and design fluency, but not the other domains; and its indirect effects were only significant on visual memory, word and color processing speed through ipsilateral infarcts. After adjustment of education and vascular risk factors, only the direct effects of Rt-CAS on design fluency and its indirect effects on visual memory through Rt-infarct were abolished.

Discussion

In this study, our results further substantiated the general notion that CAS can lead to cognitive impairments through multiple mechanisms. In good agreement with previous findings, we found the CAS severity was correlated with its ipsilateral PVL, DWML, and infarct severity, but not the contralateral ones, suggesting the effects of CAS on leukoaraiosis and infarcts might be lateralized (Baradaran et al., 2017; Benli et al., 2021). In correlation analyses, either left or right CAS severity were correlated with most cognitive tests. The lateralization effect on cognition from unilateral carotid stenosis was further demonstrated by mediation analyses in that left and right CAS were associated with verbal and non-verbal cognitive functions, respectively. Moreover, we observed the cognitive sequalae directly predicted by CAS severity, and indirectly through left periventricular leukoaraiosis and ipsilateral infarcts, suggesting CAS-associated leukoaraiosis and infarcts might play a mediating role in impairments in different specific cognitive domains.

Indirect effects of carotid artery stenosis

Leukoaraiosis

Leukoaraiosis is associated with carotid atherosclerosis, and it has been recognized as a risk for cognitive impairment in both neurodegenerative and vascular diseases (Saba et al., 2009; Price et al., 2012; Lucatelli et al., 2016; Sam et al., 2016). In this study,

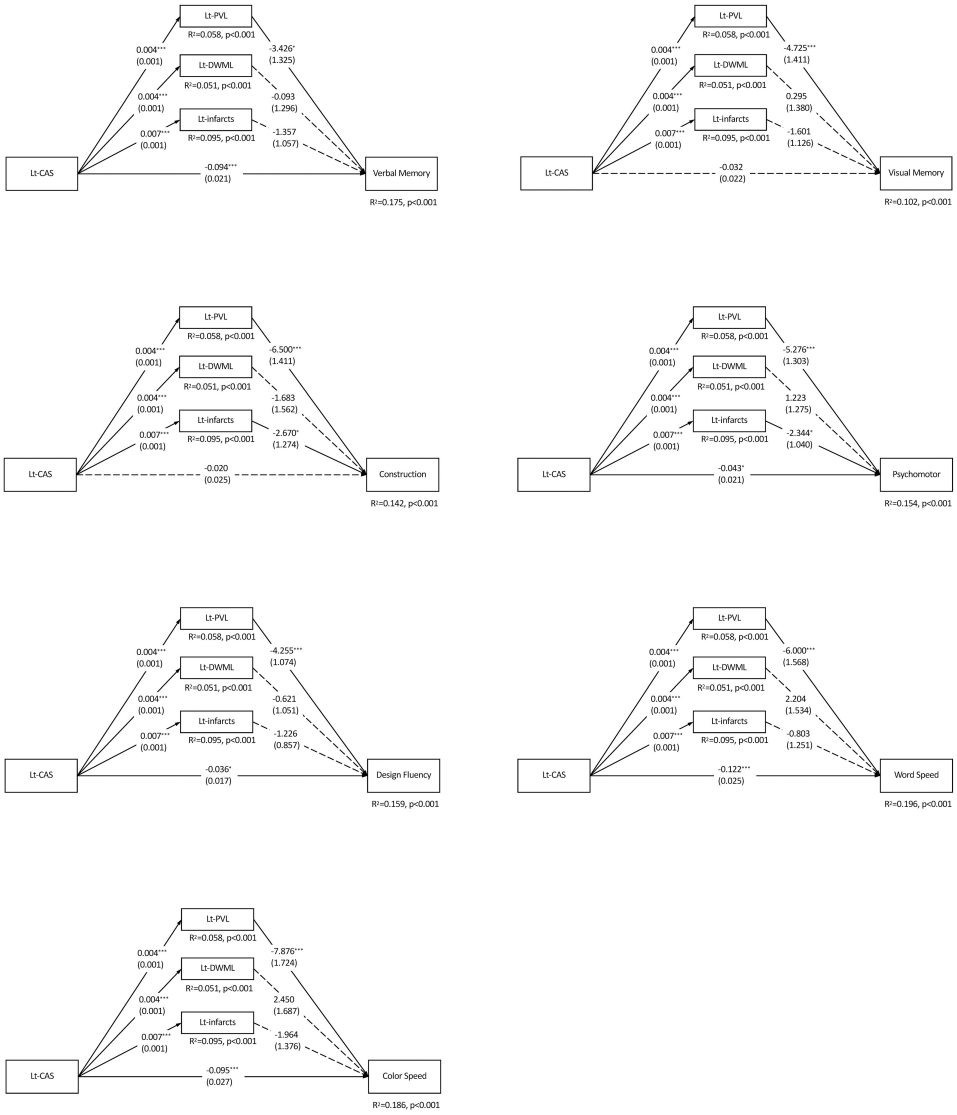

FIGURE 2
Parallel mediation models of each specific cognitive domain predicted by the left carotid artery stenosis and ipsilateral leukoaraiosis and infarcts. *N* = 226. The value in each path is the regression coefficient (standard error). Lt, left; CAS, carotid artery stenosis; PVL, periventricular leukoaraiosis; DWML, deep white matter leukoaraiosis; R^2, coefficient of determination. $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

the negative indirect effects of Lt-CAS through Lt-PVL were prevalent and significant on most cognitive domains even after adjustment of education and vascular risk factors. The findings were in agreement with an earlier review suggesting that PVL has negative impacts on cognitive abilities (Bolandzadeh et al., 2012; Wiggins et al., 2019). However, there was general lack of indirect effects of Rt-CAS through Rt-PVL and Rt-DWML on any specific cognitive domains. One possible reason was that the ipsilateral PVL severity in Lt-CAS happened to be more severe than that of Rt-CAS (**Supplementary Table B**), and some have argued that cognitive impairments can be attributed to leukoaraiosis only when the leukoaraiosis severity exceeds certain thresholds (Zeng et al., 2019).

Leukoaraiosis has great diversity in spatial distribution and signal intensity, and various leukoaraiosis quantification methods have been developed (Pantoni et al., 2002; Rost et al., 2014). Our study applied Fazekas scale to evaluate leukoaraiosis severity, as it is one of the well-established visual rating scales and also has good agreement with other visual scoring systems (Pantoni et al., 2002). Visual rating scales can be easily and reliably administered in clinical practice, and they have been proved to provide valuable prognostic information (Verdelho et al., 2012; Rudilosso et al., 2019). However, visual rating scales typically allow for a small number of ordinal ratings, and they may have limited sensitivity to subtle changes as compared

TABLE 4 Effects of unilateral carotid artery stenosis on specific cognitive domains in parallel mediation analyses.

		Predictor (Left carotid artery stenosis, %)				Predictor (Right carotid artery stenosis, %)			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
Domains		**Effect (SE)**	**95%CI**	**Effect (SE)**	**95%CI**	**Effect (SE)**	**95%CI**	**Effect (SE)**	**95%CI**
Verbal memory	*Total*	−0.117 (0.020)	**[−0.156, −0.078]**	**−0.085 (0.020)**	**[−0.123, −0.046]**	**−0.053 (0.021)**	**[−0.094, −0.012]**	−0.018 (0.021)	[−0.059, 0.022]
	Direct	**−0.094 (0.021)**	**[−0.136, −0.053]**	**−0.074 (0.021)**	**[−0.115, −0.034]**	−0.034 (0.022)	[−0.078, 0.010]	−0.0001 (0.003)	[−0.054, 0.032]
	Indirect								
	PVL	**−0.0135 (0.007)**	**[−0.028, −0.002]**	−0.004 (0.004)	[−0.014, 0.002]	−0.005 (0.005)	[−0.016, 0.002]	−0.0001 (0.003)	[−0.006, 0.005]
	DWML	−0.0004 (0.005)	[−0.011, 0.010]	0.001 (0.004)	[−0.009, 0.010]	0.001 (0.006)	[−0.010, 0.014]	0.002 (0.004)	[−0.005, 0.012]
	Infarct	−0.009 (0.007)	[−0.024, 0.004]	−0.007 (0.006)	[−0.020, 0.004]	−0.014 (0.009)	[−0.032, 0.002]	−0.009 (0.008)	[−0.025, 0.005]
		R^2 = 0.175, F = 11.726***		R^2 = 0.264, F = 9.743***		R^2 = 0.077, F = 4.630**		R^2 = 0.205, F = 7.002***	
Visual memory	*Total*	**−0.060 (0.022)**	**[−0.103, −0.018]**	−0.020 (0.021)	[−0.061, 0.021]	**−0.094 (0.021)**	**[−0.135, −0.053]**	**−0.069 (0.020)**	**[−0.109, −0.029]**
	Direct	−0.032 (0.022)	[−0.076, 0.012]	−0.009 (0.021)	[−0.051, 0.034]	**−0.069 (0.022)**	**[−0.112, −0.026]**	**−0.057 (0.021)**	**[−0.099, −0.015]**
	Indirect								
	PVL	**−0.019 (0.007)**	**[−0.035, −0.006]**	−0.005 (0.004)	[−0.016, 0.001]	−0.005 (0.004)	[−0.013, 0.002]	−0.0001 (0.002)	[−0.004, 0.004]
	DWML	0.001 (0.006)	[−0.010, 0.013]	0.001 (0.001)	[−0.010, 0.011]	−0.003 (0.006)	[−0.015, 0.009]	−0.003 (0.004)	[−0.012, 0.004]
	Infarct	−0.010 (0.007)	[−0.026, 0.003]	−0.005 (0.006)	[−0.020, 0.006]	**−0.018 (0.009)**	**[−0.037, −0.006]**	−0.010 (0.008)	[−0.026, 0.005]
		R^2 = 0.102, F = 6.255***		R^2 = 0.225, F = 7.854***		R^2 = 0.143, F = 9.184***		R^2 = 0.263, F = 9.668***	
Construction	*Total*	−0.030 (0.025)	[−0.080, 0.020]	0.008 (0.025)	[−0.042, 0.057]	−0.042 (0.025)	[−0.091, 0.007]	−0.016 (0.025)	[−0.066, 0.034]
	Direct	0.020 (0.025)	[−0.030, 0.070]	0.039 (0.025)	[−0.011, 0.088]	−0.025 (0.026)	[−0.076, 0.027]	−0.014 (0.026)	[−0.065, 0.038]
	Indirect								
	PVL	**−0.026 (0.009)**	**[−0.045, −0.011]**	**−0.012 (0.007)**	**[−0.026, −0.001]**	−0.008 (0.006)	[−0.023, 0.002]	−0.0002 (0.005)	[−0.010, 0.009]
	DWML	−0.007 (0.006)	[−0.021, 0.004]	−0.006 (0.006)	[−0.019, 0.003]	−0.008 (0.007)	[−0.024, 0.004]	−0.005 (0.006)	[−0.018, 0.003]
	Infarct	**−0.017 (0.009)**	**[−0.037, −0.001]**	−0.013 (0.008)	[−0.031, 0.0003]	−0.001 (0.011)	[−0.024, 0.020]	0.003 (0.009)	[−0.016, 0.021]
		R^2 = 0.142, F = 9.178***		R^2 = 0.210, F = 7.225***		R^2 = 0.093, F = 5.651***		R^2 = 0.173, F = 5.680***	
Psychomotor	*Total*	**−0.075 (0.020)**	**[−0.115, −0.035]**	**−0.047 (0.020)**	**[−0.087, −0.006]**	**−0.083 (0.020)**	**[−0.122, −0.043]**	**−0.054 (0.021)**	**[−0.095, −0.014]**
	Direct	**−0.043 (0.021)**	**[−0.084, −0.003]**	−0.31 (0.021)	[−0.072, 0.010]	**−0.063 (0.021)**	**[−0.104, −0.023]**	**−0.048 (0.021)**	**[−0.089, −0.006]**
	Indirect								
	PVL	**−0.021 (0.007)**	**[−0.036, −0.008]**	**−0.011 (0.006)**	**[−0.023, −0.001]**	−0.007 (0.006)	[−0.020, 0.002]	−0.0002 (0.004)	[−0.010, 0.008]
	DWML	0.005 (0.005)	[−0.006, 0.016]	0.004 (0.005)	[−0.005, 0.015]	−0.003 (0.006)	[−0.016, 0.008]	−0.002 (0.004)	[−0.011, 0.006]
	Infarct	**−0.015 (0.008)**	**[−0.032, −0.002]**	−0.009 (0.007)	[−0.024, 0.003]	−0.009 (0.009)	[−0.028, 0.009]	−0.005 (0.008)	[−0.021, 0.011]
		R^2 = 0.154, F = 10.052***		R^2 = 0.202, F = 6.869***		R^2 = 0.159, F = 10.472***		R^2 = 0.205, F = 6.989***	
Design fluency	*Total*	**−0.063 (0.017)**	**[−0.096, −0.030]**	**−0.033 (0.016)**	**[−0.065, −0.001]**	**−0.064 (0.016)**	**[−0.096, −0.031]**	**−0.039 (0.016)**	**[−0.071, −0.007]**
	Direct	**−0.036 (0.017)**	**[−0.069, −0.002]**	−0.019 (0.017)	[−0.051, 0.014]	**−0.043 (0.017)**	**[−0.076, −0.009]**	−0.030 (0.017)	[−0.063, 0.003]

(Continued)

10.3389/fnagi.2022.972480

TABLE 4 (Continued)

Domains		Predictor (Left carotid artery stenosis, %)				Predictor (Right carotid artery stenosis, %)			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
		Effect (SE)	95%CI	Effect (SE)	95%CI	Effect (SE)	95%CI	Effect (SE)	95%CI
	Indirect								
	PVL	**−0.017 (0.006)**	**[−0.030, −0.007]**	**−0.007 (0.004)**	**[−0.016, −0.0002]**	−0.005 (0.004)	[−0.014, 0.002]	−0.0001 (0.003)	[−0.006, 0.005]
	DWML	−0.002 (0.004)	[−0.012, 0.005]	−0.002 (0.004)	[−0.011, 0.005]	−0.003 (0.005)	[−0.014, 0.005]	−0.002 (0.003)	[−0.010, 0.004]
	Infarct	−0.008 (0.005)	[−0.018, 0.003]	−0.005 (0.004)	[−0.014, 0.003]	−0.012 (0.007)	[−0.026, 0.001]	−0.007 (0.006)	[−0.020, 0.004]
		$R^2 = 0.159$, $F = 10.462$***		$R^2 = 0.252$, $F = 9.150$***		$R^2 = 0.154$, $F = 10.060$***		$R^2 = 0.257$, $F = 9.383$***	
Word PS	*Total*	**−0.143 (0.024)**	**[−0.190, −0.096]**	**−0.110 (0.024)**	**[−0.157, −0.064]**	−0.045 (0.025)	[−0.095, 0.004]	−0.011 (0.025)	[−0.060, 0.038]
	Direct	**−0.122 (0.025)**	**[−0.171, −0.073]**	**−0.105 (0.024)**	**[−0.153, −0.056]**	−0.013 (0.026)	[−0.064, 0.039]	−0.007 (0.026)	[−0.044, 0.058]
	Indirect								
	PVL	**−0.024 (0.008)**	**[−0.041, −0.010]**	**−0.009 (0.005)**	**[−0.021, −0.0004]**	−0.008 (0.006)	[−0.022, 0.002]	−0.0002 (0.003)	[−0.007, 0.007]
	DWML	0.008 (0.006)	[−0.004, 0.021]	0.004 (0.005)	[−0.006, 0.016]	0.008 (0.008)	[−0.005, 0.025]	0.004 (0.005)	[−0.004, 0.017]
	Infarct	−0.005 (0.009)	[−0.024, 0.011]	−0.001 (0.007)	[−0.017, 0.013]	**−0.034 (0.012)**	**[−0.058, −0.011]**	**−0.022 (0.010)**	**[−0.043, −0.004]**
		$R^2 = 0.196$, $F = 13.438$***		$R^2 = 0.270$, $F = 10.010$***		$R^2 = 0.104$, $F = 6.441$***		$R^2 = 0.213$, $F = 7.334$***	
Color PS	*Total*	**−0.129 (0.027)**	**[−0.182, −0.076]**	**−0.096 (0.027)**	**[−0.149, −0.042]**	**−0.116 (0.027)**	**[−0.169, −0.064]**	**−0.091 (0.027)**	**[−0.144, −0.037]**
	Direct	**−0.095 (0.027)**	**[−0.149, −0.041]**	**−0.080 (0.028)**	**[−0.134, −0.026]**	**−0.080 (0.027)**	**[−0.134, −0.026]**	**−0.070 (0.028)**	**[−0.125, −0.015]**
	Indirect								
	PVL	**−0.031 (0.010)**	**[−0.054, −0.013]**	**−0.015 (0.008)**	**[−0.033, −0.001]**	−0.010 (0.007)	[−0.026, 0.003]	−0.0003 (0.005)	[−0.012, 0.011]
	DWML	0.010 (0.007)	[−0.003, 0.024]	0.006 (0.006)	[−0.004, 0.019]	0.005 (0.008)	[−0.008, 0.023]	0.002 (0.005)	[−0.007, 0.014]
	Infarct	−0.013 (0.010)	[−0.033, 0.005]	−0.007 (0.008)	[−0.025, 0.008]	**−0.032 (0.013)**	**[−0.061, −0.007]**	**−0.023 (0.012)**	**[−0.047, −0.001]**
		$R^2 = 0.186$, $F = 12.580$***		$R^2 = 0.227$, $F = 7.978$***		$R^2 = 0.182$, $F = 12.321$***		$R^2 = 0.232$, $F = 8.179$***	

$N = 226$. Values in adjusted columns represent the estimated effects, standard errors, and 95% confidence intervals by using years of education, hypertension, hyperlipidemia and diabetic mellitus as the covariates. Total effect of carotid artery stenosis on each specific cognitive domain is the sum of direct and indirect effects, which is equal to the estimate of regressing each specific cognitive domain on carotid artery stenosis on either side, respectively. The direct effect of carotid artery stenosis on each specific cognitive domain was estimated while the parallel mediators being remained constant. PVL, periventricular leukoaraiosis; DWML, deep while matter leukoaraiosis; SE, standard error; CI, confidence interval; PS, processing speed; R^2, coefficients of determination of the parallel mediation models. Significant estimated effects of predictors (carotid artery stenosis on each side, respectively) are presented in bold typeface.

**$p < 0.01$; ***$p < 0.001$.

10.3389/fnagi.2022.972480

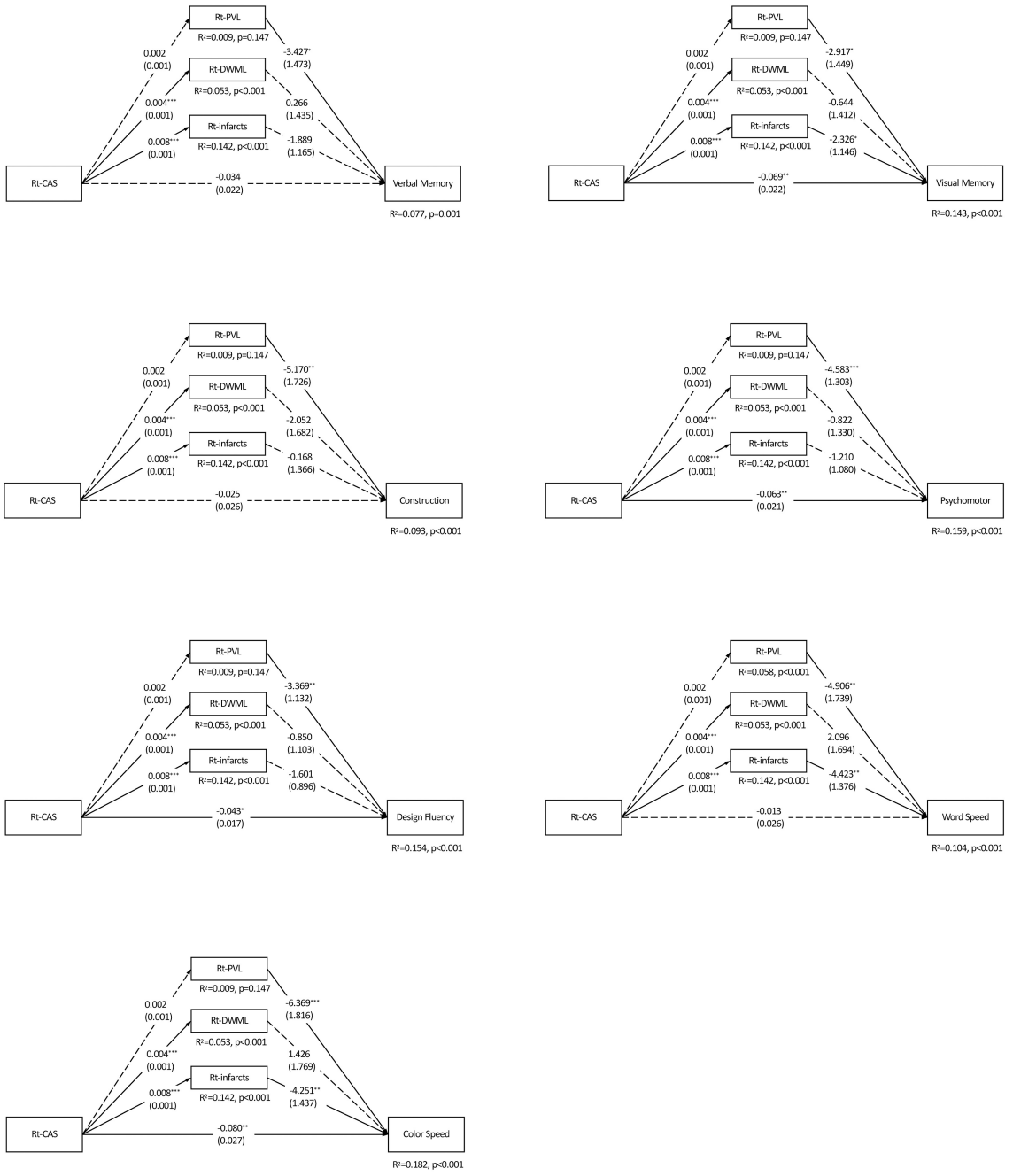

FIGURE 3
Parallel mediation models of each specific cognitive domain predicted by the right carotid artery stenosis and ipsilateral leukoaraiosis and infarcts. N = 226. The value in each path is the regression coefficient (standard error). Rt, right; CAS, carotid artery stenosis; PVL, periventricular leukoaraiosis; DWML, deep white matter leukoaraiosis; R^2, coefficient of determination. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Significant estimated effects of predictors (carotid artery stenosis on each side, respectively) are presented in bold typeface.

to voxel-based volumetric quantification (Lambert et al., 2016; Garnier-Crussard et al., 2022). Therefore, voxel-based volumetric quantification methods might be able to provide more delicate information as to leukoaraiosis evolution in response to medical and intervention treatment in future studies.

Infarcts

Similar to leukoaraiosis, the severity of infarcts was also relatively mild (medians = 0 for both sides) in this study. Despite the infarct severity was negatively associated with nearly all cognitive domains in simple correlation analyses, their cognitive effects were greatly diminished in the mediation models.

Although the relationships between infarcts and cognitive performance have been well-documented (Sigurdsson et al., 2017; Weaver et al., 2021), it is possible the influences of infarcts on cognitive domains might be balanced out because more than 50% of all participants who were infarct-free in this study (**Supplementary Table B**).

Direct effects of carotid artery stenosis

Many studies have shown grade of CAS is inversely associated with cognitive performance (Wang et al., 2016; Porcu et al., 2020). In fact, cognition is a generic term encompassing various specific intellectual abilities, which are not only vulnerable to heterogeneous brain pathologies, but also strongly associated with demographic and vascular risk factors (Cheng et al., 2020; Desideri and Bocale, 2021). Our study findings were in line with previous studies showing that Rt-CAS was more closely related to non-verbal functions, whereas Lt-CAS tended to associate with more pervasive cognitive domains (Huang et al., 2014, 2017, 2018). The lateralization cognitive effects of unilateral CAS remained after controlling for education and multiple vascular risk factors. On the other hand, CAS severity could only be deemed as a proxy indicator of cerebral chronic hypoperfusion as collateral blood supply from the circle of Willis or ophthalmic artery may ameliorate cerebral hemodynamics. Therefore, incorporation of perfusion information in the mediation models would further differentiate the cognitive effects from LVD and SVD pathologies in future studies.

Limitations

This study might represent one of few attempts to bring multiple pathophysiological factors together for exploring the possible underlying mediators on the associations between CAS and cognition, yet it had several limitations. First, the major contributors (brain perfusion status and hemodynamics) to cognitive impairments in patients with CAS were not included for analyses. Although some participants with CAS had the perfusion data available in this study, inadequate sample size might render inclusion of perfusion data for mediation analyses inappropriate. Second, the non-CAS group was recruited to contrast the CAS effects on cognition. However, their educational attainments and other vascular risk factors were different from the CAS groups, which could only be taken into account by statistical adjustment. Third, even though the severity in leukoaraiosis and infarcts in the participants of this study were relatively mild, their mediating effects were still detectable in this study. As leukoaraiosis and infarct severity are diverse in CAS patients, generalization of the present results should be cautious. Moreover, the variances of individual specific cognition domains could be accounted for by the variables included in this study appeared modest. In fact, cognition can be influenced by many pathogeneses beyond the present selection. It is deemed necessary to have a comprehensive inclusion of potential risk factors for mediation analysis in future study.

In conclusion, unilateral CAS would aggravate ipsilateral leukoaraiosis and infarct severity. Left and right CAS would predominantly lead to verbal and non-verbal cognitive impairment respectively, and such effects could be mediated through CAS-related leukoaraiosis and infarct. Given that cognition is subject to heterogenous pathologies, the exact relationships between LVD and SVD markers and their composite prognostic effects on cognition require further investigation.

Data availability statement

The datasets presented in this article are not readily available because the used consent does not allow for the public sharing of the data. Requests to access the datasets should be directed to M-YH, myho@mail.cgu.edu.tw.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Chang Gung Memorial Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

K-LH wrote a portion of the manuscript, revised the initial draft, performed neurologic examinations, and took part in the data collection and analysis and scientific interpretation of data. T-YC, Y-JC, H-CW, and C-HL performed the data collection, neurologic examination, and scientific interpretation of data. Y-MW performed MRI analysis and had scientific interpretation of data. T-HL conceptualized the study design, took part in critical review of the manuscript, and edited the manuscript for content. M-YH conceptualized the study design, wrote the initial draft, conducted the cognitive evaluation, and carried out statistical analyses and critical review of the manuscript. All authors critically reviewed the manuscript and approved the final version for publication.

Funding

This study was supported from Research Fund of Chang Gung Memorial Hospital (CMRPG3J1193 and BMRP611) and

Ministry of Science and Technology, Taiwan (MOST 103-2410-H-182-002-MY2, MOST 107-2410-H-182-008-MY3, and 110-2314-B-182A-073-MY3).

Acknowledgments

We thank Clinical Trial Center of Chang Gung Memorial Hospital for administrative assistance under support from the Ministry of Health and Welfare, Taiwan.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.972480/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Systematic Review
PUBLISHED 25 October 2022
DOI 10.3389/fnagi.2022.1012870

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 06 August 2022
ACCEPTED 28 September 2022
PUBLISHED 25 October 2022

CITATION
Cansino S (2022) Brain connectivity changes associated with episodic recollection decline in aging: A review of fMRI studies.
Front. Aging Neurosci. 14:1012870.
doi: 10.3389/fnagi.2022.1012870

Brain connectivity changes associated with episodic recollection decline in aging: A review of fMRI studies

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With advancing age, individuals experience a gradual decline in recollection, the ability to retrieve personal experiences accompanied by details, such as temporal and spatial contextual information. Numerous studies have identified several brain regions that exhibit age-related activation differences during recollection tasks. More recently, an increasing number of studies have provided evidence regarding how brain connectivity among the regions supporting recollection contributes to the explanation of recollection deficits in aging. However, brain connectivity evidence has not been examined jointly to provide an integrative view of how these new findings have improved our knowledge of the neurofunctional changes underlying the recollection deficits associated with aging. Therefore, the aim of the present study was to examine functional magnetic resonance imaging (fMRI) studies that employed one of the numerous methods available for analyzing brain connectivity in older adults. Only studies that applied connectivity analysis to data recorded during episodic recollection tasks, either during encoding or retrieval, were assessed. First, the different brain connectivity analysis methods and the information conveyed were briefly described. Then, the brain connectivity findings from the different studies were described and discussed to provide an integrative point of view of how these findings explain the decline in recollection associated with aging. The studies reviewed provide evidence that the hippocampus consistently decreased its connectivity with the parahippocampal gyrus and the posterior cingulate cortex, essential regions of the recollection network, in older adults relative to young adults. In addition, older adults exhibited increased connectivity between the hippocampus and several widespread regions compared to young adults. The increased connectivity was interpreted as brain intensification recourse to overcome recollection decay. Additionally, suggestions for future research in the field are outlined.

KEYWORDS

recollection, familiarity, functional connectivity, effective connectivity, task-related brain connectivity

Introduction

Brain connectivity has been extensively analyzed during resting-state conditions and less when the brain is performing a task. The discovery that spontaneous brain connectivity occurred between brain regions that are associated with specific cognitive demands (e.g., Beckmann et al., 2005) or the finding that some of these brain regions decrease their activity when they are engaged in a cognitive task, such as the default mode network (e.g., Raichle et al., 2001), have provided evidence that resting-state connectivity might play an important role in brain integration, a condition that may be important for preserving cognitive functioning in aging (for reviews see Antonenko and Flöel, 2014; Sala-Llonch et al., 2015). However, spontaneous brain connectivity may be a cause or an effect of cognitive functioning. This issue is difficult to solve because these findings are based only on correlational evidence. Thus, the analysis of brain connectivity while the brain is engaged in a specific cognitive task represents a direct opportunity to examine which regions are actually involved in performing the task and how each other interacts to reach the task goal under conditions of both success and failure. This information is crucial to investigate topics such as age-related cognitive decay, which requires a more detailed explanation to provide or suggest possible solutions. This is particularly important for the case of episodic memory, the type of memory that is considered to be the most affected by the aging process (Nyberg et al., 2012).

Episodic memory is the ability to remember our personal past (Tulving, 1972). Because each of our experiences occurred in a specific context, the capability to retrieve contextual details, such as the location, moment or emotion that accompanied the experience, is conceived as truly episodic and evidence that the memory has been retrieved by means of recollection. This process has been distinguished from familiarity, the ability to remember personal events that lack any contextual detail and provide only a vague awareness that the experience has previously occurred (Mandler, 1980). Moreover, consistent evidence indicates that only recollection is severely affected with advancing age, whereas familiarity is only slightly diminished (Spencer and Raz, 1995; e.g., Cansino et al., 2013). Therefore, to investigate how brain connectivity during episodic memory might be modified in older adults, it is essential to examine studies that reliably assess recollection. For example, the old/new task that is frequently used to examine episodic memory does not allow disentangling whether correct old items had been identified by means of recollection or familiarity. Thus, studies that employed this task will not be included in the present review. Therefore, only functional magnetic resonance imaging (fMRI) studies that examined brain connectivity while participants were engaged in a recollection task were reviewed.

Several brain connectivity analyses have been developed that provide distinctive and a wide range of information on how the brain functions as a network. For a detailed description of these analyses, see Friston (2011). A brief description of the brain connectivity analyses more frequently used is provided below, and most of the methods were employed by the studies reviewed here. Studies of brain structural connectivity, which refers to the neural anatomical connection within the brain, known as the connectome (Sporns et al., 2005), will not be discussed in the current review. Brain connectivity analytic methods are able to measure functional connectivity or effective connectivity. The former measures the dependency between neural events using statistical tests, such as correlation, covariance or coherence. Conversely, effective connectivity provides evidence of the influence that a neural unit, either unicellular or multicellular, exerts over other units within the neural system under examination (Friston, 2011). Effective connectivity allows determining the direction of influence between brain elements because it is based on dynamic activity models that take into account information, such as the anatomical connections between neural units and the simultaneous interaction of the elements within the model (Friston, 2011).

The effects of aging on brain connectivity have been previously reviewed for several cognitive functions in task-related and resting-state studies (Antonenko and Flöel, 2014; Sala-Llonch et al., 2015); thus, these reviews discuss brain connectivity in aging related to cognition in general. Two reviews have focused on brain connectivity associated with episodic memory. One of these reviews (Palacio and Cardenas, 2019) included task-related and resting-state studies performed in healthy adults between 18 and 65 years old. However, no distinction was made regarding participants' age, and brain connectivity results in task-related and resting-state studies were discussed jointly without distinguishing their different contributions to episodic memory. The other review (Jeong et al., 2015) covered studies in task-related and resting-state conditions with healthy young adults and adults affected by different pathologies, such as Alzheimer's disease or mild cognitive impairment; however, only one positron emission tomography (PET) study in healthy older adults was included. Therefore, no previous review has exclusively analyzed the effects of aging on brain connectivity during episodic memory, particularly during recollection.

Numerous episodic memory fMRI studies have identified several brain regions that exhibit activation changes associated with aging. Evidence from these studies has provided valuable information regarding the network that is responsible for encoding and retrieving personal memories and the specific brain regions that may be affected by the aging process. However, little is known about how the connectivity among the brain regions that comprise this episodic memory network is affected by aging. Although various studies on the topic have emerged in the last two decades and their findings have significantly

enlightened the subject, their contributions have remained dispersed in the literature. Therefore, the purpose of the present review is to integrate those findings and analyze them jointly to provide a comprehensive view of how brain connectivity within the episodic memory network changes as a consequence of aging.

Connectivity analysis

Functional connectivity is often measured by means of pairwise correlations between time series activity in specific brain regions. However, when the interest is to analyze the potential connectivity among several brain regions, other methods are more suitable, such as psychophysiological interaction (PPI) or seed partial least square (seed PLS). PPI allows the identification of regions across the whole brain, the activity of which is related to that of a seed region in a specific task, group or experimental condition (Friston, 2011). However, PPI does not provide information about the direction of the connectivity between the seed and the brain regions with which it relates and only provides information about the strength of the regression between their activities (O'Reilly et al., 2012). When the interest is to test the psychological factor for more than two conditions, the generalized psychophysiological interaction (gPPI) offers the possibility of creating a PPI term for each condition in the study (McLaren et al., 2012). Seed PLS is a multivariate analysis that was introduced to the examination of fMRI data by McIntosh et al. (1996). PLS identifies brain regions in the whole brain that interact among each other or with specific seeds or regions of interest (ROIs) within each experimental condition or contrast (Krishnan et al., 2011). To assess functional connectivity, the seed mean signal is correlated with the activity of all the other voxels within each condition and across participants (McIntosh, 1999). PLS generates a latent variable for each condition that indicates the pattern of connectivity with the seed that distinguishes each condition.

Graph theory is a collection of mathematical structures used to describe the organization of brain networks or of any other type of network in nature. The topology of a network model is described by its elements or nodes and by the interaction among these elements or edges (Sporns, 2014). The local or global organization of the network is assessed through descriptive analyses applied to the nodes and edges. To build a brain network, first, the nodes should be defined by dividing the brain into regions mostly based on anatomic or functional principles; then, functional connectivity or edges between nodes are defined by using neuronal time series cross-correlation or any other statistic demonstrating their dependency (Rubinov and Sporns, 2010). However, this interaction does not guarantee that nodes are structurally connected (Zalesky et al., 2012). Graph theory provides some useful network parameters, such as the small-worldness topography organization, which refers to a model that has short paths. Fewer edges are required to connect two nodes and have high clustering, i.e., the degree to which nodes within a cluster are connected (Watts and Strogatz, 1998). These properties allow efficient global and local information transmission within the network (Liao et al., 2017). Another characteristic of a network is its density, which refers to the number of edges with respect to the maximum possible edges that the model can comprise (Liao et al., 2017). In brain networks, density may represent its linking cost to functioning.

Effective connectivity can be measured through structural equation modeling (SEM). SEM is able to examine causality between brain regions and how this influence may vary across experimental conditions or groups. This is achieved because SEM applied to fMRI data takes into account brain regions that are anatomically connected and information about how these regions interact with each other (McIntosh and Gonzalez-Lima, 1994). Then, the covariance or the degree to which the activities between two regions jointly vary is estimated simultaneously with that of other brain regions, i.e., taking into account the influence of other brain regions within the model (McIntosh and Gonzalez-Lima, 1994). Path coefficients represent the direction and connectivity strength between brain regions in the network.

Dynamic causal modeling (DCM), which is another method used to measure effective connectivity, estimates the interaction among brain regions and how they are influenced by experimental conditions. DCM models the rate of change in neural activity relative to time as a consequence of an input signal from an external stimulation or another brain region (Friston et al., 2003). The analysis assumes that the influence that one region exerts over another region occurs after a certain delay (Kahan and Foltynie, 2013); thus, DCM estimates the present state and the immediate future state of a dynamic system. The method consists of specifying plausible realistic models comprised of structurally connected brain regions, the brain region that receives the driving-input or experimental stimulation, and the coupling among regions that are modulated by experimental task conditions. Then, observer data are used to estimate the coupling parameters of the model, i.e., the strength and direction of the interaction among regions. Bayesian model selection is used to select the model that provides the best fit and parsimonious model.

Method

A systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for all fMRI articles that examined functional or effective connectivity in healthy older adults while participants were performing a recollection task during encoding, retrieval or both phases. Figure 1 displays the systematic review flowchart. All articles were indexed in PubMed, and the publication date was not limited. The search

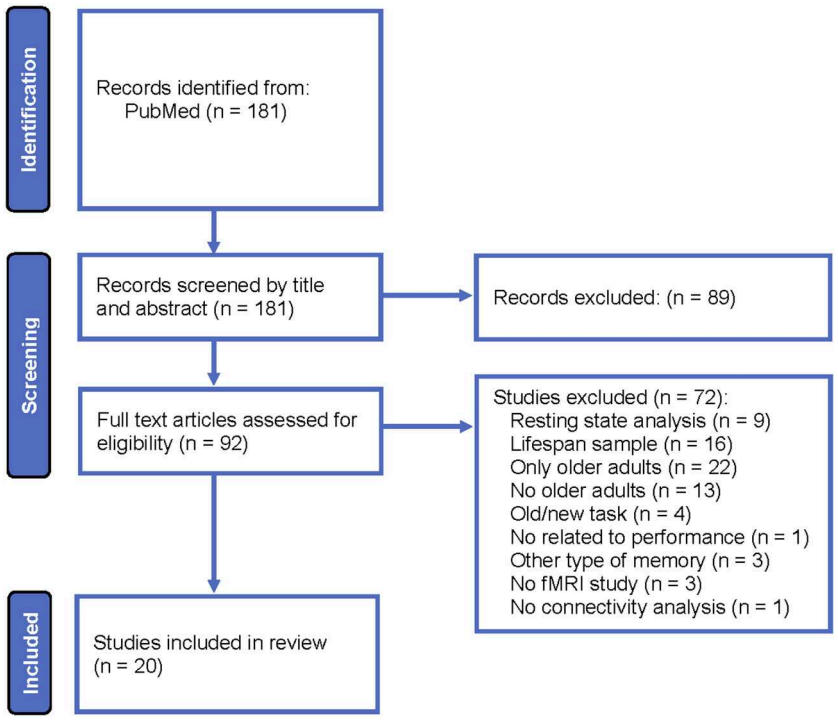

FIGURE 1
Systematic review flowchart.

was performed with the following key words: functional magnetic resonance imaging, fMRI, brain connectivity, functional connectivity, effective connectivity, episodic memory, recollection, aging, older adults, and elderly. The results were filtered to exclude studies that included non-healthy adults.

The following eligibility criteria were employed: (i) fMRI studies that included healthy older adults and young adults and (ii) functional or effective connectivity analyses of data recorded during a recollection task. The following exclusion criteria were employed: (i) studies that analyzed brain connectivity during the resting state, (ii) studies in lifespan samples without distinguishing connectivity result differences between young and older adults, (iii) connectivity analyses not related to memory performance, (iv) studies that employed old/new recognition tasks, and (v) studies that did not include young adults. Note that studies that included young, middle-aged, and older adults were incorporated in the current review, but the results obtained in the middle-aged group were not reviewed.

Results

A total of 20 studies were eligible for inclusion in this review. Table 1 displays the main characteristics of these studies, such as sample size, participants' mean age, and standard deviations when available. The studies in each table were listed in chronological order based on the year of publication. Brain connectivity was analyzed during encoding in five studies, during retrieval in 10 studies and in both phases in five studies. Effective connectivity was analyzed in only four of the studies, and all the rest employed functional connectivity procedures.

Table 2 depicts the type of stimuli employed in each study and the task used during encoding and retrieval. Almost all studies used neutral stimuli, with the exception of three studies that used words or images with positive or negative emotional valence. Recollection was examined using associative tasks in six studies, source memory tasks in six studies and a variety of tasks that included the description of a picture or an event or the imagination of an event, among several others.

The contrast used by each study to analyze connectivity is described in Table 3. The main brain connectivity findings obtained in each study are displayed in Table 4. The specific ROIs or seeds used in each study are shown where available. This table depicts whether connectivity or other parameters increased or decreased in older adults relative to young adults. Remarkably, 11 studies used the hippocampus as an ROI or seed, and two more reported findings related to this brain region. The other region that was the second most often used as an ROI or seed or that showed significant connectivity results was the amygdala. This region was used in three studies.

TABLE 1 Characteristics of studies included in the review, listed in chronological order.

	Sample *n*: age (years, *M* ± SD)		Phase	Analysis	
	Young	Older			
Daselaar et al. (2006)	12: 22.2 ± 2.5	12: 69.2 ± 7.6	Ret	Correlation	FC
Dennis et al. (2008)	14: 19.4 ± 1.3	14: 68.4 ± 7.1	Enc	Correlation	FC
St Jacques et al. (2009)	15: 24.8 ± 4.7	15: 70.2 ± 5.3	Enc	Correlation	FC
Tsukiura et al. (2011)	20: 21.0 ± 3.4	20: 68.6 ± 3.7	Ret	Correlation	FC
Dew et al. (2012)	17: 23.7	14: 66.2	Ret	PPI	FC
Matthäus et al. (2012)	10: 26.3 ± 2.7	10: 67.8 ± 4.0	Ret	Graph theory	FC
St Jacques et al. (2012)	14: 24.4 ± 3.7	14: 64.2 ± 2.9	Ret	DCM	EC
Waring et al. (2013)	19: 23.7	18: 74.4	Enc	SEM	EC
Fandakova et al. (2015)	28: 24.9 ± 1.8	30: 72.3 ± 2.0	Ret	PPI	FC
Grady et al. (2015)	15: 25.6 ± 5.1	15: 69.8 ± 4.7	Ret	Seed PLS	FC
Legon et al. (2016)	14: 26.0	15: 63.0	Enc	DCM	EC
Cansino et al. (2017)	22: 23.4 ± 1.8	22: 67.1 ± 2.7	Enc/Ret	DCM	EC
King et al. (2018)	36: 22.2 ± 3.0	64: 68.4 ± 3.6	Ret	PPI	FC
Monge et al. (2018)	15 19.5 ± 1.3	40: 68.6 ± 6.4	Ret	Graph theory	FC
Ankudowich et al. (2019)	45: 26.1	44: 66.6	Enc/Ret	Seed PLS	FC
Stark et al. (2020)	31: 29.0	31: 76.0	Enc/Ret	Correlation	FC
Varangis et al. (2021)	73: 28.3 ± 4.0	84: 71.2 ± 4.1	Enc/Ret	Graph theory	FC
Deng et al. (2021)	21: 23.5 ± 3.0	20: 70.5 ± 5.4	Ret	Graph theory	FC
Tsuruha and Tsukiura (2021)	29: 22.5 ± 1.7	24: 66.0 ± 3.1	Ret	gPPI	FC
Ness et al. (2022)	48: 26.4 ± 4.2	43: 67.3 ± 5.7	Enc	gPPI	FC

Enc, encoding; Ret, retrieval; PPI, psychophysiological interaction; DCM, dynamic causal models; SEM, structural equation modeling; PLS, partial least squares; gPPI, generalized psychophysiological interaction; FC, functional connectivity; EC, effective connectivity.

Some brain region connectivity analyses were reported more frequently across studies, as noted for the superior parietal cortex and adjacent areas (5 times), superior occipital cortex and adjacent areas (4 times), dorsolateral prefrontal cortex (PFC) (4 times), ventrolateral PFC (3 times), orbitofrontal cortex (3 times), cingulate (3 times), and parahippocampal cortex (3 times). Across studies, connectivity was analyzed among 39 different brain regions that yielded significant results related to aging. However, given that most of the studies included similar regions, a total of 76 brain region connectivity analyses showed significant results associated with the aging process.

Connectivity between the hippocampus and several brain regions was observed in 13 out of 20 studies included in the present review. However, a different pattern of connectivity was observed in older adults compared to young adults depending on the brain region with which the hippocampus interacted. To illustrate these findings, Figure 2 shows brain regions (parahippocampal gyrus, posterior cingulate, amygdala, anterior temporal lobe, and putamen) for which connectivity with the hippocampus decreased in older adults relative to young adults. Conversely, Figure 3 depicts brain regions (superior PFC, dorsolateral PFC, orbitofrontal cortex, anterior cingulate, precuneus, superior occipital cortex, inferior parietal cortex, caudate, and inferior frontal gyrus) for which connectivity with the hippocampus increased in older adults compared to young adults. Finally, Figure 4 displays brain regions (superior parietal cortex, superior temporal gyrus, and ventrolateral PFC) for which connectivity with the hippocampus was not consistent. Some studies reported a connectivity increase in older adults relative to young adults, and others reported a connectivity decrease. The brain regions displayed in the figures were identified with the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), and the figures were created with the software Mango (ric.uthscsa.edu/mango; Multi-image Analysis GUI).

Discussion

The relatively few studies that have examined age-related brain connectivity changes while participants attempt to encode or retrieve information from episodic memory by means of recollection processes have provided relevant and consistent information that improves our understanding of the transformations that may occur within the episodic memory

TABLE 2 Tasks used in the studies included in the review, listed in chronological order.

	Stimuli	Encoding task	Retrieval task
Daselaar et al. (2006)	Words	Outside the scanner. English word/non-English word	Old/new, confident rate: 1 low/4 high
Dennis et al. (2008)	Faces-scenes	N-back task ($n = (2)$	Definitely old, probably old or new
St Jacques et al. (2009)	Pictures: positive, negative, neutral	Valance rating: positive, negative or neutral	Outside the scanner. Associative: Detail description of the picture after a cue word
Tsukiura et al. (2011)	Faces, names, job titles	Sex judgment of faces	Associative: Selection of the name associated with the face from two learned names, selection of the job title associated with the face from two learned job titles
Dew et al. (2012)	Words	Pleasant/unpleasant Concrete/abstract	Source memory: Select judgment performed in encoding: pleasantness/concreteness
Matthäus et al. (2012)	Words		Personal word or not, then vivid imagination of the cue event
St Jacques et al. (2012)	Words: positive, negative		Retrieve in detail an autobiographic memory trigger by the word, emotion rate:−4 negative/+4 positive, reliving rate: 1 low/8 high
Waring et al. (2013)	Images (positive, negative, neutral)- over neutral scenes	Approach/stay/retreat	Outside the scanner. Old/new for images and scenes presented separately.
Fandakova et al. (2015)	Word-word	Living/nonliving	Continuous recognition: the word-word was presented for the first time (sure new, unsure new) or for the second time (sure old, unsure old)
Grady et al. (2015)	Photographs, cue words		Source memory: Questions about elements from the picture: two options, I do not know
Legon et al. (2016)	Image-image	Detail orientation: anything red? Context orientation: in a kitchen? Response: yes/no	Outside the scanner. Associative: Same or rearranged, yes/no and certainty
Cansino et al. (2017)	Images	Natural/artificial	Source memory: Select the quadrant where each image was presented at encoding
King et al. (2018)	Word-word	Select the object denoted by the words that fit into the other	Associative: Select same pairs, rearranged pairs or new pairs
Monge et al. (2018)	Words	Outside the scanner. Pleasant/unpleasant Bigger/smaller than a shoebox	Source memory: probably pleasantness or size, definitely pleasantness or size
Ankudowich et al. (2019)	Faces	Pleasant/neutral	Source memory: Select the face presented at the left or at the right at encoding, easy task (three face pairs), hard task (six face pairs).
Stark et al. (2020)	Images	Continuous incidental encoding: indoor/outdoor	Repeated, similar and new images No memory task was required.
Varangis et al. (2021)	Words		Logical memory, word order and paired associates
Deng et al. (2021)	Pictures, labels	Label representativeness rate: 1 low/4 high	Associative: Detail recollection of the picture that accompanied the label, memory detail rate: 1 low/4 high
Tsuruha and Tsukiura (2021)	Words	Stimuli were presented in a videoclip by a person belonging to the same age group or different age group	Source memory: Same age group, different age group, new
Ness et al. (2022)	Image-face, image-place	Imagination of an interaction between item-face or face-place, vividness rate: 1 low/4 high	Outside the scanner. Associative: (20 min or six days after encoding; select the face (four options) or the place (four options) that accompanied the image

TABLE 3 Contrast employed to analyze recollection in each study included in the review, listed in chronological order.

Daselaar et al. (2006)	A quasi- exponential function based on old responses with confident rate 4 vs. old responses with confident rates 1, 2 or 3
Dennis et al. (2008)	Subsequent definitely old responses vs. subsequent likely old and new responses
St Jacques et al. (2009)	Negative pictures subsequently remembered minus subsequently forgotten vs. neutral pictures subsequently remembered minus forgotten
Tsukiura et al. (2011)	Hits during the retrieval of names and job titles vs. misses
Dew et al. (2012)	Context cue trials without memory test vs. correct context trials
Matthäus et al. (2012)	Block design: Time series recorded during episodic memory demands
St Jacques et al. (2012)	Modulatory inputs: 50% more episodic richness than semantic details from verbally retrieved memories from the scanner session within two days later
Waring et al. (2013)	Subsequently remembering item and background vs. subsequently remembering item, for positive and negative scene valences
Fandakova et al. (2015)	Correct rejection of rearranged pairs vs. correct rejection of novel pairs
Grady et al. (2015)	Incorrect and I do not know answers vs. correct answers
Legon et al. (2016)	Modulatory inputs: *F*-contrast over detail and context orientation conditions at encoding
Cansino et al. (2017)	Modulatory inputs: subsequent recollection vs. subsequent unsuccessful recollection; recollection vs. unsuccessful recollection
King et al. (2018)	Hits for intact pairs vs. rearranged pairs judged as intact (false alarms)
Monge et al. (2018)	High confident hits for source memory
Ankudowich et al. (2019)	Orthogonal polynomial contrasts for encoding and retrieval: Retrieval accuracy vs. right PFC vs. left hippocampus
Stark et al. (2020)	Time series across the entire scan, independent of task condition
Varangis et al. (2021)	Time series concatenated from the three episodic memory task
Deng et al. (2021)	High memory based on memory detail rates 3 and 4; low memory based on memory detail rates 1 and 2
Tsuruha and Tsukiura (2021)	Hit source for same age group; Hit source for different age group
Ness et al. (2022)	Subsequent durable memories (6 days after) vs. subsequent transient memories (20 min after)

PFC, prefrontal cortex.

network. This notion is particularly true in the case of the hippocampus because its connectivity with several brain regions has been extensively assessed across studies. These results are discussed in detail. Specifically, the mechanism by which the hippocampus modifies its connectivity with other brain regions in older adults compared to young adults is described.

Based mainly on PET and fMRI activation studies, several authors have outlined brain regions that may encompass the episodic memory network. For example, Markowitsch (1995) proposed that the encoding network of episodic memory remains mainly on the hippocampus, cingulate, thalamus, association areas and dorsolateral prefrontal cortex, whereas the retrieval network includes the hippocampal gyrus, medial PFC, orbitofrontal cortex, ventrolateral PFC, and anterolateral temporal cortex. Other authors (Skinner and Fernandes, 2007) proposed that the episodic memory network involved in both familiarity and recollection comprises the medial temporal lobe, sensory regions, parietal, and prefrontal cortices; however, recollection may be distinguished from familiarity by recruiting more areas within these regions. A specific recollection network has also been proposed that includes the hippocampus, lateral parietal region, parahippocampus, anterior medial PFC, and posterior cingulate (Yonelinas et al., 2005). This network is conceived as a core recollection network that is involved independent of the stimulus modality or the task employed to measured recollection (Rugg and Vilberg, 2013).

The brain networks described are highly coincident and clearly illustrate the brain regions that have been more consistently identified as supporting episodic memory. However, brain connectivity analyses, especially those that freely allow the discovery of brain regions interacting across the whole brain, have identified additional regions involved in recollection. Thus, the findings from these studies expand our current knowledge of the regions underlying recollection and especially of those regions in which connectivity is altered by aging. These additional regions are outlined in the following discussion. Given that the effects of aging on brain connectivity could manifest as a connectivity decrease between brain regions or other network parameters or as a connectivity increase between brain regions or other parameters, the following discussion is divided into those brain regions that showed a connectivity decrease, increase or both with the hippocampus as a consequence of aging.

TABLE 4 Brain connectivity results reported in the studies included in the review, listed in chronological order.

	ROI/seed	Results in older adults relative to young adults
Daselaar et al. (2006)	Hippocampus Rhinal cortex	↓ Hippocampus—Retrosplenial cortex, left parietotemporal cortex ↑ Rhinal cortex—PFC
Dennis et al. (2008)	Left hippocampus	↓Occipitotemporal cortex, parahippocampal gyrus, superior parietal, thalamus, hypothalamus, posterior cingulate ↑ Ventrolateral PFC, superior PFC, mid-dorsolateral PFC, orbitofrontal cortex, cingulate gyrus
St Jacques et al. (2009)	Amygdala	↓ Ventrolateral PFC, left hippocampus ↑ Dorsolateral PFC, fusiform gyrus, posterior parietal cortex
Tsukiura et al. (2011)		↓ Hippocampus—left anterior temporal lobe
Dew et al. (2012)	Left hippocampus	↓ Red nucleus ↑ Superior temporal gyrus, inferior frontal gyrus, anterior cingulate, precentral gyrus
Matthäus et al. (2012)		↓ Small-worldness, left—right occipital lobes, left—right parietal lobes, hippocampus—amygdala ↑ Density and size network, left parietal—left frontal regions
St Jacques et al. (2012)	Hippocampus, ventrolateral PFC	↓ Modulation ventrolateral PFC → hippocampus
Waring et al. (2013)	Several ROIs	↑Positive orbitofrontal ↔ dorsolateral PFC, positive orbitofrontal ↔ amygdala, negative amygdala ↔ fusiform, positive fusiform ↔ superior parietal lobe
Fandakova et al. (2015)	Left anterior PFC	↑ Right postcentral, parahippocampal and middle temporal gyri in older adults whose activation patterns deviate less from that of young adults
Grady et al. (2015)	Inferior frontal operculum and anterior insula	= No significant task-related connectivity differences between young and older adults in episodic memory
Legon et al. (2016)	Right hippocampus, visual association area, right inferior frontal gyrus	↓ Modulation of the inferior frontal gyrus → visual association area ↑ Modulation of the inferior frontal gyrus → hippocampus
Cansino et al. (2017)	Superior occipital gyrus, hippocampus, orbitofrontal cortex	↑ Modulation superior occipital gyrus ↔ hippocampus ↔ orbitofrontal cortex ↔ superior occipital gyrus during successful encoding and retrieval ↓ Negative driving input of the occipital cortex during successful encoding
King et al. (2018)	Left angular gyrus, medial PFC, left hippocampus, left middle temporal gyrus, posterior cingulate cortex	↓ Average correlations between pairs of anatomical brain regions, except for hippocampus; average correlations between pairs of functional brain regions, except for medial PFC; average connectivity change across all seed and target pairs that exhibited a main effect of age group
Monge et al. (2018)		↑ Widespread functional connections at the medial temporal lobe nodes in the source memory task
Ankudowich et al. (2019)	Right dorsolateral PFC, left hippocampus	↑ Positive hippocampus—bilateral dorsolateral PFC, superior parietal cortex, precuneus, ventral occipital cortex, left inferior parietal cortex, cingulate cortex, negative related to retrieval accuracy
Stark et al. (2020)	Six hippocampal segmentations, parahippocampal cortex, perirhinal cortex, entorhinal cortex	↓ Hippocampus—parahippocampal cortex; three anterior hippocampus regions—parahippocampal cortex
Varangis et al. (2021)		= No significant connectivity metric differences noted between young and older adults in episodic memory
Deng et al. (2021)		↑ Functional integration of PFC with the remainder of the brain network, that was associated with better performance; reconfiguration of connectivity patterns in PFC ↓ Reconfiguration in medial temporal lobe
Tsuruha and Tsukiura (2021)	Right hippocampus, right anterior temporal lobe	↓ Hippocampus, anterior temporal lobe—posterior superior temporal sulcus for words encoded by a person from a different age group
Ness et al. (2022)	Left hippocampus, putamen, caudate	↓ Hippocampus—putamen, caudate for durable memories (six days retention) ↑ Hippocampus—caudate associated with higher durable memory performance

When more than one ROI or seed was used, the specific ROI or seed showing significant results is indicated in the result column.
PFC, prefrontal cortex, ↑ increased, ↓ decreased, or = no change in connectivity or other parameters in older adults relative to young adults,—no direction, → forward, backward, **or** ↔ bidirectional connectivity.

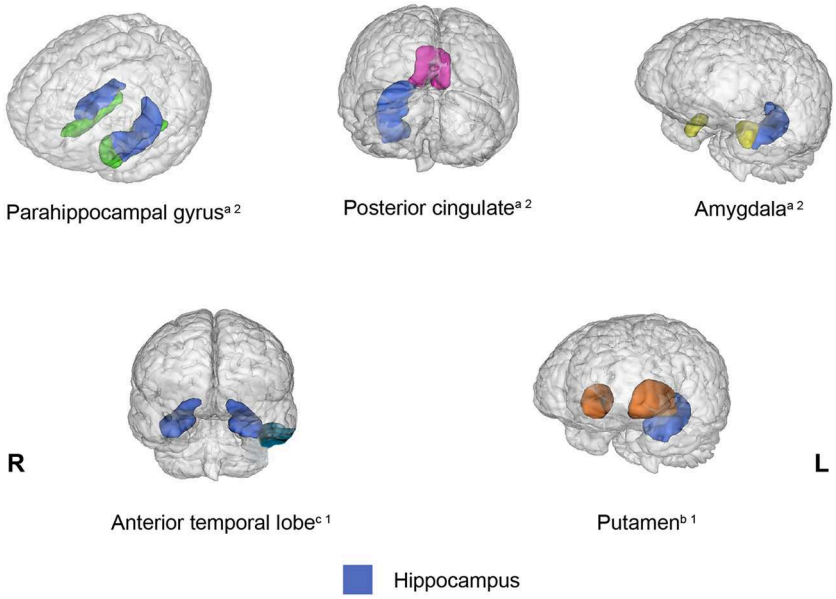

FIGURE 2
Brain regions that showed decreased connectivity with the hippocampus in older adults relative to young adults across the studies reviewed. When the connectivity was reduced bilaterally, the brain region was displayed in both hemispheres. [a]Brain regions that exhibited reduced connectivity with the hippocampus during encoding and retrieval. [b]Brain regions that displayed reduced connectivity with the hippocampus during encoding. [c]Brain regions that showed reduced connectivity with the hippocampus during retrieval. [1]One study showed this result. [2]Two studies showed this result.

Decreased connectivity

Activation fMRI studies have frequently interpreted underactivation in healthy older adults compared to young adults as evidence that older adults are unable to allocate sufficient activity from brain regions relevant for the task (Logan et al., 2002), probably due to the employment of other strategies. However, multiple interpretations are conceivable for an observed connectivity decrease in older adults relative to young adults. Certainly, low connectivity between brain regions indicates less transmission of information. However, this reduction in connectivity may be noted because the information has not been processed to a level that is appropriate for transmission and therefore remains at the original brain region to be further processed. Another possibility is that unfeasible information was transmitted that was unsuitable for processing by the receptive brain region. Another alternative is that the region responsible for transmitting the information did not receive the appropriate information in the first place. It is also possible that the information was transmitted but did not reach the appropriate brain region. Another option is that a functional reorganization has occurred, and other brain regions are processing the appropriate information. Although it is impossible to disentangle these possibilities with the information at hand, the intention is to acknowledge the diversity of reasons why brain connectivity may fail.

The hippocampus is certainly the most crucial brain region that supports episodic memory, as demonstrated in several lesion studies in humans and other species and in fMRI experiments (for a review see Squire et al., 2004). Therefore, the hippocampus may be conceived as the key component that operates within the widespread episodic memory network that gives rise to our ability to remember our own experiences. The reviewed studies found that the connectivity between the hippocampus and the following regions diminished in older adults: parahippocampal gyrus (Dennis et al., 2008; Stark et al., 2020) posterior cingulate (Daselaar et al., 2006; Dennis et al., 2008), amygdala (St Jacques et al., 2009; Matthäus et al., 2012), anterior temporal lobe (Tsukiura et al., 2011), and putamen (Ness et al., 2022). All these regions have been included in at least one of the networks reviewed above, except for the amygdala and putamen. The retrosplenial cortex, which also exhibits reduced connectivity with the hippocampus in older adults relative to young adults (Daselaar et al., 2006), is often combined with the posterior cingulate cortex because both regions are sensitive to the amount of information recollected (Rugg and Vilberg, 2013).

All these regions share a common feature. Specifically, these regions share a relative anatomical proximity to the hippocampus without any tendency to be in any particular location relative to the hippocampus, such as anterior or posterior. Moreover, the structural connection between the hippocampus and all these regions has been confirmed

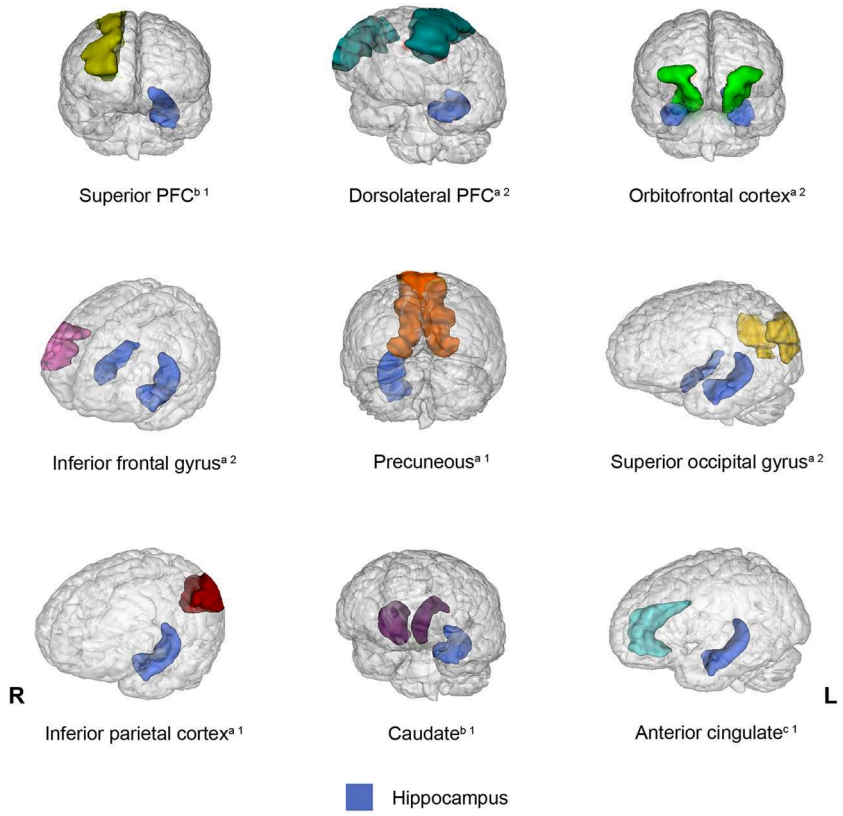

FIGURE 3
Brain regions that showed increased connectivity with the hippocampus in older adults relative to young adults across the studies reviewed. When the connectivity was increased bilaterally, the brain region was displayed in both hemispheres. [a]Brain regions that exhibited increased connectivity with the hippocampus during encoding and retrieval. [b]Brain regions that displayed increased connectivity with the hippocampus during encoding. [c]Brain regions that showed increased connectivity with the hippocampus during retrieval. [1]One study showed this result. [2]Two studies showed this result.

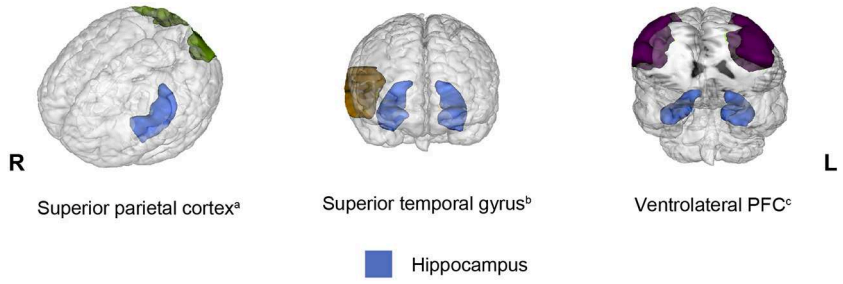

FIGURE 4
Brain regions that showed opposite results regarding decreased and increased connectivity with the hippocampus in older adults relative to young adults across the studies reviewed. When connectivity was observed bilaterally, the brain region was displayed in both hemispheres. All opposite results involved two studies. [a]Brain regions that exhibited opposite results during encoding. [b]Brain regions that displayed opposite results during retrieval. [c]Brain regions that showed opposite results in different phases.

using superresolution diffusion MRI (Maller et al., 2019). The parahippocampal cortex is an essential element of the recollection network because it is involved in encoding and retrieving contextual information (Diana et al., 2007). The content of recollection representations is initially sustained by the posterior cingulate and then is transmitted to frontal areas to receive further monitoring and examination (Yonelinas et al., 2005). The role of the anterior temporal lobe in recollection

is more controversial because damage to this region has been associated not only with retrograde amnesia but also with semantic memory impairment (Markowitsch, 1995). Although the amygdala has not been conceived as a component of the recollection network, extensive evidence has confirmed that the amygdala modulates memory consolidation (McGaugh, 2004) but not exclusively episodic memory. The putamen contributes to motor execution and motor learning as well as episodic memory, as revealed by several recent studies (for a review see Ell et al., 2011). Specifically, it has been suggested that the putamen interacts with the hippocampus during episodic memory formation.

Reduced connectivity between the hippocampus and the parahippocampal cortex (Dennis et al., 2008; Stark et al., 2020), posterior cingulate (Daselaar et al., 2006; Dennis et al., 2008), and amygdala (St Jacques et al., 2009; Matthäus et al., 2012) was observed during encoding and retrieval. Connectivity reduction between the hippocampus and anterior temporal lobe was observed during retrieval (Tsukiura et al., 2011), whereas connectivity reduction between the hippocampus and the putamen was observed during encoding (Ness et al., 2022). However, because these two last findings were examined in only one phase, either during encoding or retrieval, it is unknown whether this result is exclusive to one of the phases or both. The parahippocampal and posterior cingulate cortices are probably the most relevant regions that showed decreased connectivity with the hippocampus because they belong to the core recollection network. Levels of activation in the hippocampus, parahippocampal gyrus, and posterior cingulate were reported in only one of the studies reviewed (Dennis et al., 2008). Lower activation in older adults than in young adults was observed in the first two regions but not in the posterior cingulate. Thus, the decreased connectivity between the hippocampus and the parahippocampal gyrus may be attributed to the fact that the information was not processed to an optimal level to be transmitted.

According to Eichenbaum et al. (2007), contextual information is formed and represented in the parahippocampal cortex during encoding. Then, this information is transmitted to the hippocampus, where item and context are integrated for episodic representation. In contrast, during retrieval, the hippocampus mediates the recollection of the contextual representation allocated in the parahippocampal cortex. Therefore, the interaction between the hippocampus and parahippocampal cortex is crucial to encode and retrieve episodic representations, and the reduced connectivity between both regions clearly provides an explanation for the gradual loss of recollection in aging. The posterior cingulate is a relay area between the hippocampus and other cortical areas, such as the caudate, orbitofrontal cortex, and anterior cingulate cortex (Pearson et al., 2011). Posterior cingulate activity has been frequently identified during retrieval (e.g., Maddock et al., 2001) but also supports memory consolidation, as observed by its high degree of reinstatement activity. This finding was revealed in a study (Bird et al., 2015) in which posterior cingulate cortex activity was similar during video projection and silent video rehearsal, and this activity was related to the subsequent number of details retrieved one week later. These findings indicate the importance of the interaction between the hippocampus and posterior cingulate for recollection.

Increased connectivity

Interpreting brain overactivation in older adults relative to young adults represents a challenge in fMRI studies. Overactivation has been frequently construed as the engagement of activity from additional brain regions, not necessarily specialized to the task at hand, to compensate for neurofunctional age decline (Cabeza et al., 2002) or due to the selection of inappropriate brain regions (Buckner and Logan, 2002). A similar difficulty represents the interpretation of increased connectivity in older adults relative to young adults. Although high connectivity between regions indicates that more information is transmitted, several other explanations are possible. For example, one possibility could be that the original region has not received or processed the appropriate information; therefore, this region engenders the increase in connectivity in search of support among other regions. However, another possibility could be that spurious connectivity within the network increased the transmission of useless information that is not suitable for processing.

The studies reviewed revealed that older adults showed increased connectivity between the hippocampus and the following regions compared to young adults: the superior PFC (Dennis et al., 2008), dorsolateral PFC (Dennis et al., 2008; Ankudowich et al., 2019), orbitofrontal cortex (Dennis et al., 2008; Cansino et al., 2017), inferior frontal gyrus (Dew et al., 2012; Legon et al., 2016), inferior parietal cortex (Ankudowich et al., 2019), anterior cingulate (Dew et al., 2012), caudate (Ness et al., 2022), superior occipital cortex (Cansino et al., 2017; Ankudowich et al., 2019), and precuneus (Ankudowich et al., 2019). Interestingly, four frontal areas increased their connectivity with the hippocampus, whereas older adults attempted to recover episodic memories. However, the hippocampus also enhanced its connectivity during recollection with widespread regions. Importantly, except for the dorsolateral PFC and the orbitofrontal cortex, the remaining regions are not conceived as part of an episodic network. However, one of the networks described (Skinner and Fernandes, 2007) made reference to extensive brain areas that may include some of these regions. All these regions are structurally connected to the hippocampus (Goldman-Rakic et al., 1984; Barbas and Blatt, 1995; Catani et al., 2003; Maller et al., 2019).

During encoding, the dorsolateral PFC is engaged in the organization of information before it is encoded. During retrieval, this region is involved in monitoring and verifying the information that has been retrieved (Simons and Spiers, 2003). The orbitofrontal cortex is essential in learning associative information (Duarte et al., 2010). Lesion of the orbitofrontal cortex impairs the ability to recall contextual details of personal experiences, leading to confabulation symptoms (Gilboa et al., 2006). In healthy individuals, confabulation and context misattributions have been attributed to a lack of strategies to control recollection by constraining the memory search to the most plausible cues and retrieval routines (Burgess and Shallice, 1996), and the implementation of these strategies depends on the orbitofrontal cortex (Fischer et al., 1995). The superior PFC is activated during encoding and retrieval according to several studies (e.g., Ranganath et al., 2000); however, its specific role in episodic memory has not been elucidated. The inferior frontal gyrus activity is associated with the attempt to integrate retrieved information into rich episodic contextual associations (Lundstrom et al., 2005), and seems to control the degree of emotion enhancement when recollecting autobiographic memories (Denkova et al., 2013).

Compared to young adults, older adults showed increased connectivity between the hippocampus and the dorsolateral PFC (Dennis et al., 2008; Ankudowich et al., 2019), orbitofrontal cortex (Dennis et al., 2008; Cansino et al., 2017), and inferior frontal gyrus (Dew et al., 2012; Legon et al., 2016) during encoding and retrieval and with the superior PFC (Dennis et al., 2008) only during encoding (the only phase in which it was assessed). Although the superior PFC and the inferior frontal gyrus are not considered components of the episodic memory network, several studies provide evidence that these regions participate during recollection when the brain attempts to retrieve episodic information and when it succeeds (for a meta-analysis see Hasegawa et al., 1999). The participation of these regions during encoding may be determined by the type of processes engaged in encoding. For example, the inferior frontal cortex showed subsequent memory effects when participants performed a semantic living/nonliving judgment of words but not when they performed a phonological task, i.e., odd/even number of syllables (Otten, 2001). Damage restricted to the superior frontal gyrus impairs working memory (du Boisgueheneuc et al., 2006), and it has been demonstrated that working memory contributes to the integration of episodic representations during encoding (Plancher et al., 2018). Moreover, the brain regions that participate during encoding are also expected to participate during retrieval according to the transfer-appropriate processing principle, which assumes that memory recovery depends on the degree to which the original processes used during encoding are present during recovery (for a review see Roediger and Gallo, 2002). Thus, the studies reviewed indicate that the hippocampus interacts with regions engaged to encode and retrieve episodic information to a greater extent in older adults than in young adults.

The hippocampus also increased its connectivity with the precuneus (Ankudowich et al., 2019), and superior occipital gyrus (Cansino et al., 2017; Ankudowich et al., 2019) in older adults relative to young adults. Two regions that were not considered part of the recollection network. However, as occurs for frontal regions engaging in specific processes during encoding and retrieval, recollection also depends on brain regions specialized on the type of information, such as its modality or content. Moreover, according to cortical reinstatement, the regions involved in the encoding of such information are expected to also be activated during retrieval. Indeed, increased connectivity between the hippocampus and the precuneus and superior occipital gyrus in older adults was observed in both phases, providing support for cortical reinstatement.

Three other regions that do not belong to the recollection network also exhibited enhanced connectivity with the hippocampus in older adults compared to young adults: the anterior cingulate (Dew et al., 2012), inferior parietal cortex (Ankudowich et al., 2019), and caudate (Ness et al., 2022). The fact that it is possible to recuperate remote memories after hippocampal damage leads to the conception that the hippocampus is the initial depository of new episodic memories, but because the hippocampus constantly coordinates the reactivation of the cortical network involved in the storage of the specific features that integrate the experience, gradual memories will depend less on the hippocampus and eventually would be supported only by the cortical network (Squire and Wixtede, 2011). The anterior cingulate cortex has been identified as part of this network responsible for memory consolidation and recall of remote memories, according to several lesion studies in rodents Weible et al. (2013). The inferior parietal cortex seems to be responsible for previous mental conditions that may contribute to memory formation, such as maintaining attention on task goals and encoding salient events (for a review see Singh-Curry and Husain, 2009). Additionally, the anatomical connectivity between the hippocampus and the inferior parietal cortex has been interpreted as evidence that the former induces spatial processing in the inferior parietal cortex for memory purposes (Clower et al., 2001). World memory champions, who demonstrate outstanding performance in several memory tasks, showed high volume correlations between the hippocampus and caudate, and both volumes were positively correlated with memory performance (Müller et al., 2018). Moreover, dementia symptoms are associated with the gradual loss of projections from dopaminergic neurons into the caudate (Rinne et al., 1989). However, caudate functions are not exclusively related to memory and contribute to the selection of appropriate actions or strategies to achieve several goals (Grahn et al., 2008).

Increased connectivity between the hippocampus and the inferior parietal cortex was observed during encoding and retrieval (Ankudowich et al., 2019). However, connectivity with the caudate was reported only during encoding (Ness et al., 2022), and connectivity with the anterior cingulate was observed only during retrieval (Dew et al., 2012). However, whether these interaction enhancements exclusively occur in one phase in older adults cannot be excluded until these interactions are examined in both phases. It is crucial to understand the reason for incremental age-related connectivity between the hippocampus and several regions across the brain. One possibility could be that the hippocampus increased its connectivity within the recollection network and beyond as a compensatory mechanism (Cabeza et al., 2002). Notably, this strategy is not sufficient for older adults to compensate for their recollection deficit because their performance was below that of young adults in almost all the studies reviewed, except for studies that found no differences (Grady et al., 2015), controlled task difficulty (Daselaar et al., 2006) or did not report these data (Matthäus et al., 2012; Fandakova et al., 2015; Varangis et al., 2021). However, the lower recollection performance in older adults relative to young adults does not exclude the possibility that connectivity was enhanced as a compensatory mechanism because it is unknown whether the performance would be even lower if connectivity within the network had not increased. Another possibility could be that the hippocampus in older adults interacts with brain regions that are not properly specialized in recollection in accordance with the dedifferentiation hypothesis (Li et al., 2001). However, based on the above discussion, all the regions with which the hippocampus increased its interaction contribute in varied forms to recollection, indicating that these regions may not be conceived as inappropriate to support dedifferentiation. A more plausible explanation could be that the aging brain experiences a recollection network reorganization that adapts to the exigencies of the task at hand during encoding and retrieval by increasing the hippocampus connectivity with specific brain regions. In addition, the hippocampus also undergoes a connectivity reduction with regions conceived as essential for recollection, such as the parahippocampal cortex and the posterior cingulate.

Decreased and increased connectivity

Three regions showed opposite results across studies (i.e., either decreased or increased connectivity with the hippocampus): the superior parietal cortex (Dennis et al., 2008; Ankudowich et al., 2019), superior temporal gyrus (Dew et al., 2012; Tsuruha and Tsukiura, 2021), and ventrolateral PFC (Dennis et al., 2008; St Jacques et al., 2012); these three regions have structural connections with the hippocampus (Barbas and Blatt, 1995; Kiernan, 2012; Maller et al., 2019). Among these regions, only the ventrolateral PFC has been considered an element of the episodic memory network, particularly during retrieval. This notion is supported by various lines of evidence. Specifically, patients with damage in this area suffer from retrograde amnesia, and PET studies showed activation in this area during retrieval (Markowitsch, 1995). More recently, with the employment of repetitive transcranial magnetic stimulation (rTMS), it was observed that the direct perturbation of the ventrolateral PFC impaired the ability to retrieve details of a previous experience (Wais et al., 2018). Although the empirical evidence has confirmed that the ventrolateral PFC contributes to recollection, this region might not be conceived as part of the recollection core network because activity in this region has been linked to two broad cognitive mechanisms that contribute not only to episodic memory but also to semantic and working memory. These mechanisms include the control of strategies that guide the search for the most suitable memories and the selection of the most appropriate memory when several are retrieved (Badre and Wagner, 2007). Due to the diverse processes attributed to the ventrolateral PFC, the opposite connectivity observed between the hippocampus and this region, which seems to depend on the specific requirements of the task at hand, is understandable. Indeed, the low modulation of the ventrolateral PFC over the hippocampus was observed when older adults were required to retrieve details of previous experiences (St Jacques et al., 2012), a quite demanding task.

The superior parietal cortex does not correspond to the so-called lateral parietal cortex, which is located in the angular gyrus and considered part of the recollection network. Numerous studies (for a review, see Shomstein, 2012) have provided evidence that the superior parietal cortex is responsible for top-down attention control to relevant stimuli or features according to observer purposes. Top-down attention mechanisms exhibit opposing functions to bottom-up attention mechanisms that are guided by stimulus salience and depend on the ventral parietal cortex. A similar distinction has been proposed to explain memory retrieval, referring to the dual attentional processes hypothesis (Cabeza, 2008) or attention-to-memory hypothesis (Ciaramelli et al., 2008). According to these proposals, when memory retrieval is difficult and requires more strategies, the superior temporal lobe allocates top-down attentional resources for retrieval strategies. However, when retrieval is automatic and requires no strategies, bottom-up attentional mechanisms mediated by the ventral parietal cortex are activated to recover memories. Thus, the connectivity between the hippocampus and the superior parietal cortex may be indicative of the amount of top-down attentional resources required for the task at hand. The superior temporal gyrus is involved in several functions, such as auditory processing, language and social cognition, but its role in memory remains unknown.

The opposite connectivity observed in older adults between the hippocampus and the ventrolateral PFC (Dennis et al., 2008; St Jacques et al., 2012), superior parietal cortex (Dennis et al., 2008; Ankudowich et al., 2019), and superior temporal gyrus

(Dew et al., 2012; Tsuruha and Tsukiura, 2021) may be due to the different experimental conditions employed across studies and highlights that connectivity may not be conceived as a rigid change in one direction that occurs as a consequence of aging. In contrast, it should be expected that older adults would have decreased or increased connectivity among the recollection network and other brain regions according to task demands and the type of information that integrates the memory representation.

Conclusions and future directions

The studies reviewed provide strong evidence that the hippocampus orchestrates the brain regions that are engaged during the encoding and retrieval of episodic memory representations, as revealed by its connectivity with almost all brain regions that pertain to the recollection network or that intervene when particular task demands require processes that are attributed to specific brain regions. Moreover, the connectivity experiments reviewed disclose a pattern of how the connectivity among this network is affected by the aging process because most of the brain regions that were coupled with the hippocampus showed a consistent connectivity output in older adults, and only three of them presented opposite results.

Aging crucially changes the connectivity pattern of the recollection network, which includes the hippocampus, parahippocampus, posterior cingulate, lateral parietal cortex and medial PFC (Yonelinas et al., 2005; Rugg and Vilberg, 2013). As revealed by the findings noted across studies, the hippocampus decreased its connectivity with the parahippocampal cortex and posterior cingulate in older adults compared to young adults. None of the studies reviewed analyzed the connectivity between the hippocampus and the lateral parietal cortex and the medial PFC. Thus, whether these regions would show a similar connectivity decrease with the hippocampus remains unknown. Assuming that the parahippocampal cortex and posterior cingulate should be involved in any recollection task, their lower interaction with the hippocampus represents a crucial change that may explain the gradual loss of the ability to retrieve details of our experiences as we age.

However, the aging brain does not remain static to this loss of connectivity between the hippocampus and two essential members of the recollection network. To cope with this limitation, the aging brain seems to undergo reorganization of the recollection network that is characterized by increased interactions between the hippocampus and other regions specialized in distinctive recollection functions. In particular, the increased connectivity between the hippocampus and several PFC regions, such as the dorsolateral PFC and orbitofrontal cortex, which clearly function in encoding and retrieval, seems crucial to overcome recollection decline. The hippocampus also exhibits increased connectivity with several other regions located across the whole brain that support a variety of functions involved in recollection. However, the eventual integration of these additional brain regions within the recollection network depends on task demands, stimulus modality and contextual details. For example, one study (Dennis et al., 2008) that used the working memory n-back task to encode pairs of faces and scenes showed increased connectivity between the hippocampus and the dorsolateral PFC in older adults, a region related to the implementation of executive functions in working memory (Levy and Goldman-Rakic, 2000). Another study (Dew et al., 2012) that used a more conceptual task to encode words (pleasant/unpleasant or concrete/abstract judgments) showed increased connectivity between the hippocampus and the inferior frontal gyrus in older adults, a region that is involved when semantic judgments are required (Otten, 2001). Two studies that examined the recollection of spatial context for faces (Ankudowich et al., 2019) or images of common objects (Cansino et al., 2017) revealed increased connectivity between the hippocampus and occipital cortex in older adults compared to young adults.

Therefore, the increased connectivity observed between the hippocampus and several brain regions does not follow a rigid pattern, and the selection of these regions would depend on the task employed to process the initial information during encoding, which is expected to also be involved during retrieval according to the transfer-appropriate processing hypothesis (Kolers, 1973). Additionally, the selection of additional regions would depend on the stimulus modality or type of contextual information encoded, which are also expected to be engaged during retrieval according to the reinstatement hypothesis (e.g., Alvarez and Squire, 1994). Moreover, it is possible that all regions interact simultaneously with the hippocampus because task processing, which is uncharged mainly by PFC areas, and memory content integration require constant information fluency to update the memory representation to be encoded and retrieved. This notion is based on the reentrant signaling that occurs by reciprocal connections between separate neural groups or maps that are believed to support high brain functions (Edelman, 1993).

However, a closer look at the findings observed in the studies reviewed does not actually support drastic network reorganization in which new brain regions across the whole brain, close and distant to the hippocampus, are recruited to interact with the hippocampus and deal with recollection deficits in the aging brain. Radical neuroplasticity changes of this magnitude are not plausible, even during brain injury or learning, in which changes occur mainly in adjacent areas (Nudo, 2013). Instead, these apparently new regions are already participating in encoding and retrieval. The only difference is the magnitude to which the activity and interaction of these regions are required to achieve the task at hand. Therefore, it is proposed that the brains of young adults also recruit those regions that exhibit increased connectivity with the hippocampus in older

adults, but the connectivity with these regions is of lesser magnitude than that noted in older adults. In young adults, the processes that occur within each region, and their interaction with the hippocampus is almost negligible or below the threshold given its low intensity. Conversely, older adults require intensive utilization of those processes and more information fluency to accomplish recollection. Although overall memory performance in older adults is reduced compared with young adults, as discussed above, the connectivity analyses performed by the different studies are based on successful recollection performance, indicating that older adults succeed in those trials but at a higher cost.

Indeed, brain activity and brain connectivity differences between young and older adults are merely variances in intensity and do not imply network modifications altering brain region composition. Therefore, it is proposed that the aging brain experiences the need for intensifying processes and connectivity within the recollection network to achieve successful encoding and retrieval of rich and complex memory representation. This notion may be easily identified as brain-intensification-recourse. This mechanism seeks to counteract the natural decrease that characterizes the aging process in several domains but emerges from the need to combat the decreased connectivity observed between the hippocampus and main regions from the recollection network.

Given that most of the studies reviewed employed functional connectivity analysis, the direction of the connectivity between the hippocampus and several brain regions remains an open question. However, the studies that used effective connectivity analysis also provide information on the direction of connectivity; for example, the ventrolateral PFC diminished its modulation of the hippocampus (St Jacques et al., 2012), the inferior frontal gyrus increased its modulation of the hippocampus (Legon et al., 2016), the modulation between the hippocampus, and orbitofrontal cortex exhibited similar modulations, and between the hippocampus and superior occipital cortex increased bidirectionally during encoding and retrieval in older adults (Cansino et al., 2017). This last finding is consistent with the transfer-appropriate processing, and reinstatement hypotheses.

Thus, the specificity of these findings demonstrates the advantage of effective connectivity. Another difficulty encountered with functional connectivity is that it is based exclusively on correlation. Functional connectivity exists when two regions increase their activity above chance, and functional connectivity does not depend on the presence of a structural connection between the regions (Eickhoff and Müller, 2015). Moreover, functional connectivity between two regions may be due to another brain area wherein connectivity with those regions increases their activity (Eickhoff and Müller, 2015). Additionally, technical and biological noise may cause spurious correlations if both regions are influenced by these artifacts (Birn, 2012). Therefore, functional connectivity should be interpreted with caution.

Our knowledge of the neurofunctional changes that occur in the healthy aging brain to overcome recollection decay would benefit from the employment of connectivity analyses that provide more precise information, such as effective connectivity analyses that allow the assessment of couple direction and the presence of reciprocal connectivity. Several important questions remain unanswered. For example, confirming which brain regions belong to the recollection network and establishing the interaction sequence that these regions follow during encoding and retrieval are important future research topics. It would also be of interest to systematically examine the relevance of each region to accomplish recollection during encoding and retrieval. This information would help to identify the regions and functions that require more attention to prevent recollection decline. It is also important to precisely identify brain regions engaged during recollection according to the process involved and memory content. Additionally, it would be important to confirm that the same brain regions are involved independently of participants' age and that only the intensity of the activity and connectivity among regions varies. Of course, the answer to these questions requires the implementation of well-controlled experiments.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Funding

This work was supported by the National Autonomous University of Mexico, General Direction of Academic Personal Affairs (DGAPA) (Grant No. IG300121).

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Brief Research Report
PUBLISHED 09 November 2022
DOI 10.3389/fnagi.2022.996030

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 16 July 2022
ACCEPTED 20 October 2022
PUBLISHED 09 November 2022

CITATION
Murakami S and Lacayo P (2022) Biological and disease hallmarks of Alzheimer's disease defined by Alzheimer's disease genes. *Front. Aging Neurosci.* 14:996030. doi: 10.3389/fnagi.2022.996030

Biological and disease hallmarks of Alzheimer's disease defined by Alzheimer's disease genes

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An increasing number of genes associated with Alzheimer's disease (AD genes) have been reported. However, there is a lack of an overview of the genetic relationship between AD and age-related comorbidities, such as hypertension, myocardial infarction, and diabetes, among others. Previously, we used Reactome analysis in conjunction with the AD genes to identify both the biological pathways and the neurological diseases. Here we provide systematic updates on the genetic and disease hallmarks defined by AD genes. The analysis identified 50 pathways (defined as biological hallmarks). Of them, we have successfully compiled them into a total of 11 biological hallmarks, including 6 existing hallmarks and 5 newly updated hallmarks. The AD genes further identified 20 diverse diseases (defined as disease hallmarks), summarized into three major categories: (1) existing hallmarks, including neurological diseases; (2) newly identified hallmarks, including common age-related diseases such as diabetes, hypertension, other cardiovascular diseases, and cancers; (3) and other health conditions; note that cancers reportedly have an inverse relation with AD. We previously suggested that a single gene is associated with multiple neurological diseases, and we are further extending the finding that AD genes are associated with common age-related comorbidities and others. This study indicates that the heterogeneity of Alzheimer's disease predicts complex clinical presentations in people living with AD. Taken together, the genes define AD as a part of age-related comorbidities with shared biological mechanisms and may raise awareness of a healthy lifestyle as potential prevention and treatment of the comorbidities.

KEYWORDS

Alzheimer's disease, genetics, comorbidity, diabetes, hypertension, cancer, metabolism

Introduction

Alzheimer's disease is the major cause of dementia. According to the Centers for Disease Control and Prevention (CDC), 5.8 million Americans were living with AD in 2020 (Matthews et al., 2018). Pathological characteristics of AD include diffuse and neuritic plaques characterized by amyloid plaques and neurofibrillary tangles (Vaz and Silvestre, 2020; Sherva and Kowall, 2022). Despite these pathological characteristics, the brain pathology and progression of AD are clinically heterogeneous and thus, a clinically complex disease (Ferrari and Sorbi, 2021). Therefore, AD can be classified as late-onset (LOAD), early-onset (EOAD), and autosomal dominant forms of which LOAD is the most frequent.

AD is also highly heritable and genetically heterogeneous (Vahdati Nia et al., 2017; Sherva and Kowall, 2022). Linkage analysis, genome-wide association studies and candidate gene studies have identified Alzheimer's disease genes (AD genes). Of the 680 AD genes that are reported in the Alzgene database,[1] 356 genes were found to be associated with AD (Vahdati Nia et al., 2017). Four genes are known to cause AD (APP, PSEN1, and PSEN2) or to be a risk factor (ApoE4). Based on the AD genes, a previous study identified biological Reactome pathways as biological hallmarks (Vahdati Nia et al., 2017). Another important finding was that AD genes are associated with 5 neurological diseases, suggesting a single gene alteration can be associated with multiple forms of neurological diseases. Here we updated and organized the biological hallmarks as well as disease hallmarks. Surprisingly, the results suggest more diverse biological hallmarks and include not only neurological diseases but also common age-related diseases, which we summarize in this study.

Methods

The method has been described (Vahdati Nia et al., 2017). The AD genes have been validated and described earlier (Bertram et al., 2007; Bateman et al., 2012; Vahdati Nia et al., 2017). We used 356 AD genes. We used the updated Reactome pathway knowledgebase 2022[2] (Gillespie et al., 2022) and another knowledgebase, GeneAnalytics[3] (Ben-Ari Fuchs et al., 2016). STRING-DB (Version 11.5) was used to display gene interaction networks[4] (Szklarczyk et al., 2017). The Reactome pathways were set to a threshold of p-value $\leq$ 1.00E-05. To eliminate redundancies, we categorized the pathways into a spectrum ranging from general to specific: general Reactome pathways (general hallmarks), more specific pathways (more specific hallmarks), and specific pathways (specific hallmarks). For example, the genes involved in the transport of small molecules (e.g., minerals, proteins, lipids and fat-soluble vitamins) provided a Reactome analysis output that further ranks the order from general to specific (D'Eustachio, 2006): Transport of small molecules (as general hallmarks) → Plasma lipoprotein assembly, remodeling, and clearance (as more specific hallmarks) → Plasma lipoprotein clearance (as specific hallmarks). The Reactome results of the top detected hits of AD genes include "Plasma lipoprotein clearance" and "Plasma lipoprotein assembly, remodeling, and clearance" and thus they were combined to more specific hallmarks as "Plasma lipoprotein assembly, remodeling, and clearance." Similarly, all the redundant hits are combined and summarized. For more details of the categories are described (D'Eustachio, 2006; Reactome pathway knowledgebase, 2022).

We identified disease hallmarks, using the knowledgebase, GeneAnalytics (see text footnote 3) (Ben-Ari Fuchs et al., 2016) (Accessed on June 28, 2022). The knowledgebase uses a total of 74 databases. Of them, we used the results from 72 databases (**Supplementary Table 1**), excluding the results from 2 databases with potential reliability issues (Wikipathways and Wikipedia). The knowledgebase shows a range of p-values. We used the disease hits from the high tier with p-value $\leq$ 0.0001. The search provided the outcome as matched genes and the total genes, the latter of which included those genetically associated plus those differentially expressed in the database and thus it covers more genes than AD genes. Each disease was ranked based on the score obtained, which is based on (1) matched detected gene hits per total genes specific to each condition/quantitative trait locus; (2) the quality and the type of differentially expressed genes, genetic association and others; more details are described in the GeneAnalytics site above.

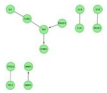
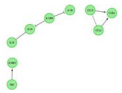
Results

We updated specific biological pathways, using the latest Reactome knowledgebase analysis (Method). A total of 50 updated pathways were identified and validated with a threshold of p-value less than 1.00E-05 (**Supplementary Table 2**). **Table 1** displays the top 10 hits sorted based on their p-value. We further eliminated the redundancies among the total 50 pathways. This process generated 11 general pathways defined as general biological hallmarks and 20 more specific pathways as defined as more specific biological hallmarks (Method). Of the 11 pathways, 5 general biological pathways are existing hallmarks reported in the earlier study (Vahdati Nia et al., 2017).

Of the 11 pathway hallmarks, 5 were newly updated hallmarks. **Figure 1** was created to display molecular interaction networks of six new hallmarks, using STRING-DB (Method). "Developmental Biology" include a subcategory in axon and

1 http://alzgene.org/
2 http://reactome.org/
3 http://geneanalytics.genecards.org/
4 http://string-db.org/

TABLE 1 Updated top 10 Reactome pathways.

General Reactome pathways	More specific pathways	Specific pathway	*P*-value	FDR	Reactome pathways	Symbols (HitGenes)
Metabolism of RNA	tRNA processing	tRNA processing in the mitochondrion	1.11E-16	1.05E-13		MT-TQ, MT-ND6, MT-ND4L, MT-ND4, MT-TT, MT-TR, MT-ND2, MT-ND3, MT-ND1, MT-TH, MT-CO2, MT-TG, MT-CO3, MT-TS2, MT-ATP6, MT-ATP8, MT-RNR1, MT-CYB
Transport of small molecules	Plasma lipoprotein assembly, remodeling, and clearance	Plasma lipoprotein assembly, remodeling, and clearance	3.33E-16	1.57E-13		LIPA, LIPC, SOAT1, CETP, APOE, A2M, ABCA1, VLDLR, LDLR, NR1H2, ABCG1, LPL, ALB, APOA1, APOA4, APOA5, NPC1, NPC2, APOC4, APOC2, APOC1
Metabolism of RNA	rRNA processing	rRNA processing in the mitochondrion	6.00E-15	1.88E-12		MT-ND4L, MT-ND4, MT-TT, MT-TR, MT-ND2, MT-ND3, MT-ND1, MT-TH, MT-CO2, MT-TG, MT-CO3, MT-TS2, MT-ATP6, MT-ATP8, MT-RNR1, MT-CYB
Immune system	Signaling by interleukins	Interleukin-4 and interleukin-13 signaling	1.94E-12	4.55E-10		ICAM1, TP53, MAOA, PIK3R1, HMOX1, CD36, IL10, IL18, IL1A, IL1B, PTGS2, ALOX5, F13A1, TNF, TGFB1, POU2F1, IL6, IL8, MMP1, MMP3, CCL2
Transport of small molecules	Plasma lipoprotein assembly, remodeling, and clearance	Plasma lipoprotein clearance	8.06E-11	1.52E-08		LIPA, LIPC, SOAT1, APOE, VLDLR, LDLR, NR1H2, APOA1, NPC1, NPC2, APOC4, APOC1
Immune system	Signaling by interleukins	Interleukin-10 signaling	3.56E-10	5.60E-08		IL1RN, ICAM1, CCR2, IL10, IL18, IL1A, IL1B, PTGS2, TNF, IL6, IL8, CCL3, CCL2
Sensory perception	Visual phototransduction	Retinoid metabolism and transport	2.00E-09	2.68E-07		LRAT, HSPG2, APOE, LDLR, LPL, APOA1, APOA4, LRP1, LRP2, LRP8, TTR, APOC2
Metabolism of proteins	Amyloid fiber formation	Amyloid fiber formation	2.98E-09	3.48E-07		APP, HSPG2, APH1A, NCSTN, APH1B, APOE, PSENEN, BACE1, CST3, ADAM10, APOA1, APOA4, TTR, SNCA, SORL1
Transport of small molecules	Metabolism of vitamins and cofactors	Metabolism of fat-soluble vitamins	5.19E-09	5.40E-07		LRAT, HSPG2, APOE, LDLR, LPL, APOA1, APOA4, LRP1, LRP2, LRP8, TTR, APOC2
Immune system	Signaling by interleukins	Signaling by interleukins	1.65E-08	1.46E-06		APP, IL1RN, ICAM1, MEF2A, TP53, MAOA, PIK3R1, HMOX1, CD36, CCR2, IL10, GSTO1, IL18, GAB2, IL1A, IL1B, PTGS2, ALOX5, IL33, F13A1, TNF, AGER, TGFB1, POU2F1, IL6, IL8, MMP1, MMP3, LCK, SOS2, CCL3, CCL2, S100B, SOD2

The Reactome analysis updated the biological pathways that we define as biological hallmarks (Accessed on June 28, 2022).
FDR (False detection rate). Hitgenes, full gene names and gene aliases are listed in Supplementary Table 3.

10.3389/fnagi.2022.996030

adipose development. Axon development was divided into EPH-Ephrin signaling and EPH-ephrin mediated repulsion of cells; the adipose development is from transcriptional regulation of white adipocyte differentiation. "Gene expression" includes RNA Polymerase II Transcription. Although "Metabolism" is an existing hallmark, eicosanoid/steroid is a new subcategory, featuring the synthesis of 5-eicosatetraenoic acids. Notably, "Metabolism of proteins" consists of the pathway directly involved in AD (amyloid formation) and two new pathways, regulation of endocrines and lifespans (regulation of IGF-1/insulin) and protein turnover (small ubiquitin-like modifiers/SUMOs). In fact, the category of SUMOylation of intracellular receptors was significantly represented by AD genes (p = value of 1.19E-06; FDR of 3.82E-05) (**Supplementary Table 3**). Interestingly, seven genes in "SUMOylation of intracellular receptors" were shared with the genes "Gene expression (RNA polymerase II transcription)"; they were AR, PPARG, PPARA, RXRA, NR1H2, VDR, and ESR1. Another hallmark includes a new category "Metabolism of RNA," which is mitochondrial tRNA and rRNA processing in mitochondria. Lastly, "Signal transduction" includes nuclear receptor signaling, including NR1H2 and NR1H3-mediated signaling, ErbB signaling and p75 NTR death signaling, while NOTCH signaling was reported previously (Vahdati Nia et al., 2017).

Figure 2A summarizes 11 general pathways defined as general biological hallmarks and 20 more specific pathways (defined as more specific biological hallmarks). The 11 general hallmarks (with keywords) are in alphabetical order [asterisks (*) indicate newly identified hallmarks]:

1. Developmental Biology (axon and adipose development)*
2. Extracellular matrix organization (protein degradation)
3. Gene expression (RNA polymerase II transcription)*
4. Hemostasis (platelet regulations)
5. Immune System (interleukins)
6. Metabolism (lipoproteins, fat-soluble vitamins, eicosanoids/steroids)
7. Metabolism of proteins (Amyloid formation, regulation of IGF-1/Insulin, and small ubiquitin-like modifiers/SUMOs)*
8. Metabolism of RNA (mitochondrial tRNA and rRNA processing)*
9. Sensory perception (retinoids)
10. Signal Transduction (ErbB, NOTCH and p75 NTR death signaling)*
11. Transport of small molecules (lipoproteins)

We further identified diseases associated with AD genes, using the GeneAnalytics knowledgebase (Method). The knowledgebase ranks the association based on 74 databases by tiers (Method). The detected gene hits of the top 20 diseases are summarized in **Table 2** (p-value $\leq$ 0.0001). Disease hallmarks are summarized in **Figure 2B**. Based on the types of diseases, the AD genes can be classified as: (1) genes specific to neurological diseases; (2) genes more general to common age-related diseases; and (3) genes general to others. The first group of diseases was neurological diseases (Alzheimer's disease, General and peripheral nervous system disease, Amyotrophic Lateral Sclerosis, Parkinson's Disease, and Schizophrenia), which were reported previously (Vahdati Nia et al., 2017). 112 AD genes were matched out of 836 AD1 genes that are either genetically associated or differentially expressed. AD1 is a specific type of AD caused by mutations in the APP gene, a source of beta-amyloid. Of a total of 356 AD genes, the gene hits of 112 accounts for 31.4% of AD genes (112 out of 356 AD genes). The second group of diseases are common age-related diseases. They include type 2 diabetes, cardiovascular diseases (myocardial infarction, heart disease, hypertension, cardiovascular system disease, and vascular disease), cancer (breast cancer, colorectal cancer, prostate cancer, and lung cancer) and others (osteoporosis). Thus, alterations in AD genes are associated with age-related comorbidities in addition to AD. The third group introduces other conditions including cystic fibrosis and quantitative trait loci (lipoprotein and body mass index). Surprisingly, cystic fibrosis is included in the disease hit by AD genes.

Discussion

This study updated genetic hallmarks for both biological Reactome pathways and those for diseases. We identified 11 general biological pathways, which included 5 existing pathways and 6 new pathways. The existing biological pathways include: The "immune system" unfolds pathways involving interleukin-4, 10, and 13 which are involved in the pathology of a wide variety of age-related diseases such as cardiovascular diseases, diabetes and cancers. Similarly, "Metabolism" includes lipoprotein dysregulations relevant to dyslipidemia, and cardiovascular diseases, among others. The previous version of Reactome knowledgebase classified retinoid metabolism as "Metabolism," yet the renewed 2022 version classified it as "Sensory perception." Retinoids or vitamin A are part of fat-soluble vitamins. Thus, we included "Sensory perception (retinoids)" back to the existing pathway of "Metabolism (fat-soluble vitamins)."

Of the 6 new biological pathways, "Metabolism of RNA" includes mitochondrial tRNA and rRNA processing in mitochondria. It may be consistent with mitochondrial deletions known to occur during aging, which may cause mitochondrial deficits (Jang et al., 2018; Swerdlow, 2018). Another category "gene expression" includes RNA Polymerase II Transcription, which is consistent with common age-related transcriptional changes (Stegeman and Weake, 2017). The category impacts the expression of a wide variety

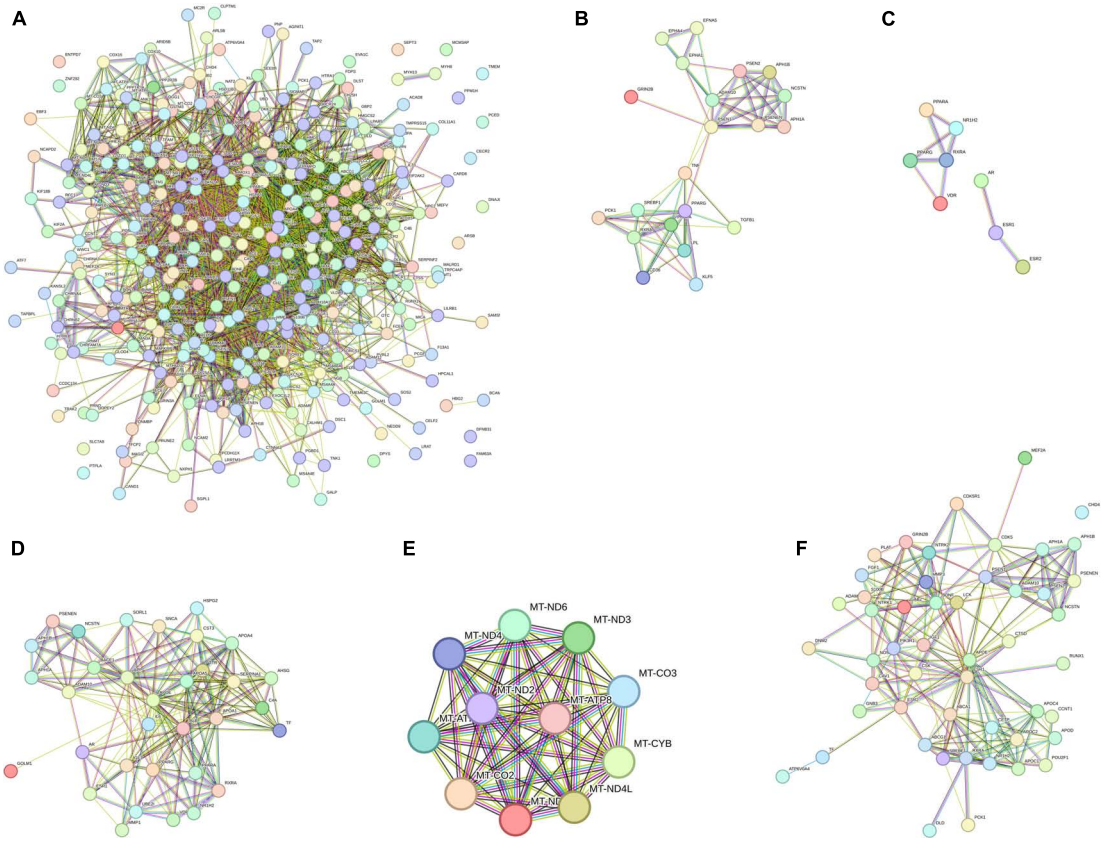


FIGURE 1
Interaction network pathways of new biological hallmarks. **(A)** Network display of all AD genes. **(B)** Developmental Biology (axon and adipose development); **(C)** gene expression (RNA polymerase II transcription); **(D)** metabolism of proteins (Amyloid formation, regulation of IGF-1/Insulin, and small ubiquitin-like modifiers/SUMOs); **(E)** metabolism of RNA (mitochondrial tRNA and rRNA processing); **(F)** signal Transduction (ErbB, NOTCH, and p75 NTR death signaling). The interaction network was created by STRING-DB. Node colors are for visual only. Edge colors are as follows: blue: from the curated database; pink: experimentally determined; black: co-expression; green: text mining.

of stress response genes (Stegeman and Weake, 2017). Related to this, stress resistance is a component of life extension in model systems (Johnson et al., 2000; Murakami, 2007; Hamilton and Miller, 2016; Buono and Longo, 2018). Metabolism eicosanoid/steroid is a new subcategory including the synthesis of 5-eicosatetraenoic acids, which is a part of the eicosanoid pathways for lipoxygenase (LOX) and cyclo-oxygenase (COX) pathways among others. The category "Metabolism of proteins," includes the pathway of amyloid formation, regulation of IGF-1/insulin, and small ubiquitin-like modifiers (SUMOs). Amyloid formation is directly involved in beta-amyloid plaques. The impaired insulin pathway causes diabetes, which is closely related to AD (Moreira, 2012; Baglietto-Vargas et al., 2016). SUMOs are involved in protein turnover which is also associated with AD (Hendriks and Vertegaal, 2016). Interestingly, SUMOylation is a post-translational modification (PTM), which controls the clearance of misfolded proteins and protein aggregations (reviewed in Vijayakumaran and Pountney, 2018). SUMOylation is involved in Alzheimer's disease (Lee et al., 2013), Parkinson's disease (Rott et al., 2017), Amyotrophic lateral sclerosis (Wada et al., 2020), Huntington's disease (Sedighi et al., 2020), Prion-like proteins (Drisaldi et al., 2015), among others. Interestingly, this study identified a subcategory of "SUMOylation of intracellular receptors" including ubiquitin-conjugating enzyme E2, UBE2I (also called UBC9). The result is consistent with the finding that AD genes are associated with a wide variety of neurodegenerative diseases, while it also implies a role of receptor-mediated gene expressions controlled by SUMOylation. However, it remains unclear about the underlying molecular mechanism. Lastly, "Signal transduction" includes nuclear receptor signaling, including NR1H2 and NR1H3-mediated signaling, ErbB cancer signaling and p75 NTR death signaling; note that NOTCH signaling was reported previously (Vahdati Nia et al., 2017). NR1H2 and NR1H3 are known as liver-X receptors (LXR), which regulate cholesterol metabolism. They are receptors for their ligands, oxysterols, that are generated by the oxidation of cholesterol through ROS (reactive oxygen species) and other processes

FIGURE 2
(A) Updated biological hallmarks. We extended the list indicated by **Table 1**, using the threshold (p-value < 1.00E-05) and summarized the 11 general biological hallmarks (circle) and more specific hallmarks (square). **(B)** Updated disease hallmarks. The diseases listed in **Table 2** are organized and grouped into 6 general disease criteria. They are further classified into: (1) neurological diseases (Alzheimer's Disease, Familial, 1, Amyotrophic Lateral Sclerosis 1, Parkinson's Disease, Late-Onset, Schizophrenia, Peripheral Nervous System Disease, Nervous System Disease, others); (2) common age-related diseases (Diabetes, Cardiovascular Disease, Cancer and Osteoporosis); and (3) other diseases (Quantitative Trait Loci and Cystic fibrosis). Note that cancers are reported to show an inverse relationship with AD genes (indicated by asterisks).

(Ma and Nelson, 2019). ErbB and p75 NTR are involved in cell survival and death.

The diseases identified by using AD genes can be categorized into 3 major criteria (neurological diseases, common age-related diseases, and others) and broken down into 6 general disease criteria. The first disease criterion is neurological diseases which include Alzheimer's disease, general and peripheral nervous system disease, amyotrophic lateral sclerosis, Parkinson's disease, and schizophrenia. This group has been reported and discussed in the previous study (Vahdati Nia et al., 2017). The study concluded that a single gene alteration may cause multiple neurological diseases. The top hit of the disease in this study was AD1 (Alzheimer's Disease, Familial, 1). Based on affected genes, the efforts on classifying AD have been ongoing and currently classified from AD1 to AD16. AD1 is caused by mutations in the APP genes. AD2 is associated with the ApoE4 allele. AD3 is caused by mutations in PSEN1. AD4 is caused by mutations in the PSEN2 gene. For more details, see the GTR (genetic testing registry) at the NCBI (National Center for Biotechnology Information database) [Genetic Testing Registry [GTR], 2022, Accessed July 12, 2022]. Due to the number of AD genes, the list of AD types is expected to be increased in number. The study provides a clear example of genetic and phenotypic heterogeneity. The result is consistent with the complex clinical presentations (i.e., clinical heterogeneity) of AD (Ferrari and Sorbi, 2021).

The second and third disease criteria include common age-related diseases. Age-related diseases are also seen in people as age-related comorbidities, with which two or more diseases commonly occur in a single person. The comorbidities include diabetes (type 2 diabetes), cardiovascular diseases (myocardial infarction, heart disease, hypertension, cardiovascular system disease, and vascular disease), cancer (breast cancer, colorectal cancer, prostate cancer, and lung cancer) and others (osteoporosis). It is worth noting that cancers show an inverse relation with AD (Nudelman et al., 2019). The observation is consistent with the previous studies that a major hypertension target, angiotensin-converting enzyme (ACE) is also involved in AD (Le et al., 2020, 2021). Despite being less defined, AD may be classified as type 3 diabetes, which is a type of diabetes in the brain (Steen et al., 2005; Pilcher, 2006; de la Monte, 2014; Leszek et al., 2017). The vast majority of AD

TABLE 2 Diverse disease hallmarks are associated with AD genes.

General criteria	Health conditions/Loci	# Matched gene hits (total genes)*
Neurological	Alzheimer's disease, Familial, 1	112 (836)
Neurological	Nervous system disease	91 (897)
Diabetes	Type 2 diabetes mellitus	84 (555)
Cardiovascular	Myocardial infarction	68 (302)
QTL*	Body mass index quantitative trait locus 11	76 (819)
Cancer	Breast cancer	73 (1,447)
Cardiovascular	Heart disease	61 (366)
Cardiovascular	Hypertension, essential	59 (457)
Cancer	Colorectal cancer	70 (1,492)
Neurological	Amyotrophic lateral sclerosis 1	55 (579)
Cardiovascular	Cardiovascular system disease	51 (192)
Neurological	Parkinson's disease, late-onset	52 (387)
Other	Lipoprotein quantitative trait locus	49 (248)
Cardiovascular	Vascular disease	44 (149)
Neurological	Schizophrenia	48 (464)
Neurological	Peripheral nervous system disease	46 (369)
Cancer	Prostate cancer	56 (1,121)
Other	Osteoporosis	44 (308)
Cancer	Lung cancer	50 (1,218)
Other	Cystic fibrosis	40 (333)

The top 20 diseases in the high tier (p-value equal or less than 0.0001) are listed. The AD gene sets in **Table 1** are used to identify diseases using all 356 AD genes (Vahdati Nia et al., 2017) and the web-based search using GeneAnalytics (Accessed on June 28, 2022).
*The number of AD gene hits (total genes classified in each group of the health conditions/Loci).

falls into LOAD, whose onset occurs starting at 65 years of age, while age-related diseases occur earlier than that. Although age-related comorbidities are known to be vulnerable to a variety of conditions, for example, COVID-19 (Antos et al., 2021), the straightforward interpretation of the result is that AD genes are associated with AD as well as with common age-related diseases.

It is conceptually important that the AD genes define AD as a part of age-related comorbidities with shared biological mechanisms. While the study raises the possibility that age-related diseases may lead to AD, we are more inclined to the possibility that the shared biological mechanisms may lead to AD and other age-related comorbidities. We are beginning to learn that "there is growing evidence that people who adopt healthy lifestyle habits. . .can lower their risk of dementia. . .which have been shown to prevent cancer, diabetes, and heart disease (Centers for Disease Control and Prevention [CDC], 2020)." Moreover, the CDC describes the broad neurological behavioral warning signs of Alzheimer's disease, such as memory impairment, difficulty in daily tasks, and poor judgment, among others [Hamilton and Miller, 2016]. This study further suggests that common age-related comorbidities may present early signs when AD genetics is involved. Related to this, a wide variety of clinical scenarios may be considered. For example, people living with AD gene alterations may have common age-related comorbidities and risk of AD development; people living with AD gene alterations may have AD with other common age-related comorbidities or people living with AD gene alterations may develop neurological and other conditions.

The cure for AD is still unknown. Currently, Aducanumab, a human anti-beta-amyloid antibody, is the only disease-modifying medication approved by FDA (U.S. Food and Drug Administration) (National Institute on Aging, 2021; Alzheimer's Association, 2022). The medication requires assessment of brain beta-amyloid, which uses PET (positron emission tomography) scans or analysis of cerebrospinal fluid. As a clinical approach to AD, we present that age-related comorbidities may provide an early assessment when genetic testing is performed. We also present that the treatment options for age-related comorbidities may be effective when biological mechanisms are considered. Alternatively, the implications from the model systems may be useful for treatment options. Stress resistance confers resistance to multiple forms of stressors, such as pathogens and the toxic beta-amyloid, which is tightly associated with Alzheimer's disease in the model systems (Florez-McClure et al., 2007; Machino et al., 2014). Multiplex stress resistance is a key to understanding the mechanism of extended lifespans and health spans (Murakami et al., 2003; Murakami, 2006). Additionally, stress resistance is tightly associated with life-extending interventions (Murakami, 2006) in which the molecular mechanisms are genetically characterized, for example, the insulin/IGF-1 pathways (Murphy and Hu, 2013), and serotonin pathways (Murakami and Murakami, 2007), among others; these can be assessed by semi-automated systems

(Machino et al., 2014). The IGF-1/insulin pathways are a major regulator of lifespans (Finch and Ruvkun, 2001; Kenyon, 2010; Ewald et al., 2018; Zhang et al., 2020) and are involved in age-related memory impairment (Murakami et al., 2005). Similarly, the serotonin pathways regulate age-related behavioral changes, lifespans and stress resistance (Murakami and Murakami, 2007; Murakami et al., 2008). More details of age-related memory impairment and a related theory (middle-life crisis theory of aging) are described elsewhere (Murakami et al., 2011; Murakami, 2013). There is an increasing number of the study using meta-analysis and GWAS (genome-wide association studies) (e.g., Jansen et al., 2019; Kunkle et al., 2019; Wightman et al., 2021; Bellenguez et al., 2022) and proteomics (Bai et al., 2020), which confirmed our earlier study (Vahdati Nia et al., 2017). This study provides an updated view of genetic and disease hallmarks. Taken together, we suggest that this study of revisiting AD genes provides the strength of treatment options as well as future direction. It will be a powerful way to develop a science-based tool for the long-waited diagnosis, prevention, and treatment options for AD.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

SM was involved in all aspects of this research. PL was involved in data analysis and presentation. Both authors contributed to the article and approved the submitted version.

Acknowledgments

This study was devoted for helping my friends and people living with Alzheimer's disease. We thank Student Doctors Timothy Balmorez and Amy Sakazaki and other Murakami lab members for discussion and comments on the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.996030/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 16 November 2022
DOI 10.3389/fnagi.2022.1010548

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 03 August 2022
ACCEPTED 27 October 2022
PUBLISHED 16 November 2022

CITATION
Wang R, Kwapong WR, Tao W, Cao L, Ye C, Liu J, Zhang S and Wu B (2022) Association of retinal thickness and microvasculature with cognitive performance and brain volumes in elderly adults.
Front. Aging Neurosci. 14:1010548.
doi: 10.3389/fnagi.2022.1010548

Association of retinal thickness and microvasculature with cognitive performance and brain volumes in elderly adults

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Background: Retinal structural and microvascular changes can be visualized and have been linked with cognitive decline and brain changes in cerebral age-related disorders. We investigated the association between retinal structural and microvascular changes with cognitive performance and brain volumes in elderly adults.

Materials and methods: All participants underwent magnetic resonance imaging (MRI), and a battery of neuropsychological examinations. Macula retinal thicknesses (retinal nerve fiber layer, mRNFL, and ganglion cell-inner plexiform layer, GCIPL) were imaged and measured with swept-source optical coherence tomography (SS-OCT) while Optical Coherence Tomography Angiography (OCTA) imaged and measured the superficial vascular complex (SVC) and deep vascular complex (DVC) of the retina.

Results: Out of the 135 participants, 91 (67.41%) were females and none had dementia. After adjusting for risk factors, Shape Trail Test (STT)-A correlated with SVC ($P < 0.001$), DVC ($P = 0.015$) and mRNFL ($P = 0.013$) while STT-B correlated with SVC ($P = 0.020$) and GCIPL ($P = 0.015$). mRNFL thickness correlated with Montreal Cognitive Assessment (MoCA) ($P = 0.007$) and Stroop A ($P = 0.030$). After adjusting for risk factors and total intracranial volume, SVC correlated with hippocampal volume ($P < 0.001$). Hippocampal volume correlated ($P < 0.05$) with most cognitive measures. Stroop B ($P < 0.001$) and Stroop C ($P = 0.020$) correlated with white matter volume while Stroop measures and STT-A correlated with gray matter volume ($P < 0.05$).

Conclusion: Our findings suggest that the retinal structure and microvasculature can be useful pointers for cognitive performance, giving a choice for early discovery of decline in cognition and potential early treatment.

KEYWORDS

retinal thickness, retinal microvasculature, cognition, magnetic resonance imaging, optical coherence tomography

Introduction

As life expectancies across the world continue to increase, there is predicted to be a rise in the global burden of age-related cognitive impairment. The economic impact of cognitive impairment across the world is tremendous (Pitkala et al., 2021). Individuals with cognitive impairment use more health care services and require greater support with daily living activities (Reppermund et al., 2013); besides individuals with cognitive impairment are at a greater risk of having anxiety, depression, and a lower quality of life (Nys et al., 2006; Hussenoeder et al., 2020). Reducing the incidence or development of cognitive impairment in the aging population is a key target for clinical trials of treatment or intervention for dementia.

Because the retina is suggested as a window to the brain, it is possible to examine early neurodegeneration and microvascular impairment in the central nervous system (CNS) (London et al., 2013). Using different ophthalmic imaging tools, studies have shown patients with dementia and mild cognitive impairment (MCI) have significantly thinner peripapillary retinal nerve fiber layer (pRNFL), macular retinal nerve fiber layer (mRNFL), and ganglion cell-inner plexiform layer (GCIPL) and/or ganglion cell complex (GCC) and microvascular impairment compared to controls without cognitive decline (Alber et al., 2020; Cheung et al., 2021). Structural retinal imaging studies on the elderly population showed thinner RNFL thicknesses and retinal microvascular impairment could indicate cognitive impairment and future cognitive decline over time ultimately resulting in an increased risk of dementia (Ko et al., 2018; Kim et al., 2022). Previous reports reported on either the retinal structure or the retinal microvasculature and its association with cognitive measures (either Montreal Cognitive Assessment, MoCA, or Mini-Mental State Examination, MMSE) in the elderly population.

Our current study aimed to explore the association between the retina (structure and microvasculature), varying array of cognitive measures, and neuroimaging parameters in healthy elderly adults without clinical dementia.

Materials and methods

The Ethics Committee of West China Hospital of Sichuan University, China, approved this study (2020-104); the protocol of this study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolling in this study.

Participants

We enrolled Chinese individuals who were 50 years or older from Chengdu, Sichuan, China as part of a healthy aging study from the Neurology Department of West China Hospital. Inclusion criteria included neurologic and neuropsychological examination with normative standards as previously reported (Casaletto et al., 2017); no major memory concerns or a diagnosed memory disorder; the capability to independently complete activities of daily living with a clinical dementia rating of 0 (Duff et al., 2022).

Participants answered questionnaires covering demographic, education, and self-reported vascular risk factors including hypertension, diabetes, smoking, and alcohol consumption information.

Neuropsychological assessment

All participants enrolled in our study underwent Shape Trail Test (STT), Chinese Rey Auditory Verbal Learning Test (C-RAVLT), and Stroop Color and Word Test (SCWT). The STT is a variant form of the classic Trail Making Test (TMT) which is widely used in China (Zhao Q. et al., 2013; Yang et al., 2021). For STT, patients underwent STT-A (drawing a line between 25 consecutive numbers as fast as possible) and STT-B (linking numbers alternating between circles and squares). SCWT consists of three cards printed in color as previously reported (Stroop, 1992; Zysset et al., 2001). It is widely used to evaluate the basic human executive function, particularly attention and information processes. The Dot subtask (card A) consists of color dots, the word subtask (card B) consists of common words unrelated to the concept of colors, and the Color-Word subtask (card C) consists of words that are names of colors. The colors used are blue, green, red, and yellow. Participants were required to name the colors in which the stimuli were printed and to disregard their verbal content. For the Chinese version (CST) of the SCWT, common Chinese characters unrelated to the concept of color were selected. Completion times and correct numbers were recorded. The Chinese Rey Auditory Verbal Learning Test (C-RAVLT) was developed to measure verbal learning and memory domain. The test consists of five successive presentations of the original list of 15 words (List A), with each trial followed by a free recall. The total number of correctly remembered words in all 5 trials was taken as the score for immediate recall (IR). Participants were required to recall words from List A again after a 30-min delay as long-delay recall (DR). Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA-BJ) (Yu et al., 2012) were also assessed for all participants. All tests were performed by a professionally trained physician.

Brain image acquisition and volumetric measures of brain structure

Image acquisition was performed using a standard 3T scanner (Siemens Skyra) with a 32- channel head coil at West

China Hospital of Sichuan University. Sequences consisted of T1 and T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI). T1-weighted high-resolution images were acquired by a 3D magnetization-prepared rapid gradient echo (MPRAGE). Imaging parameters were TR = 1,900 ms; TE = 2.4 ms; FA = 9°; FOV = 250 mm; 256 × 192 matrix; 191 slices; voxel dimension = 1.0 mm × 1.0 mm × 1.0 mm.

Computational Anatomy Toolbox 12 (CAT12)[1] was used to process T1-weighted structural images for Statistical Parametric Mapping (SPM) 12 (Wellcome Trust Center for Neuroimaging, London, UK). First, each structural image was visually inspected for artifacts and then reoriented to set the image origin at the anterior commissure. Secondly, the reoriented images were spatially normalized to Montreal Neurological Institute space and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid, using the standard tissue probability maps provided in SPM12. Then, Jacobian modulation was adjusted using volume changes induced by normalization. With modulation, voxel-based Morphometry (VBM) was considered as comparing the absolute volume of gray or white matter structures, by multiplying the spatially normalized structure by its relative volume before and after spatial normalization. Spatially normalized GM images were finally smoothed using a Gaussian kernel with a full width at half a maximum of 8 mm. Total intracranial volumes (TIVs) were calculated by summing the volume values of the GM, WM, and cerebrospinal fluid. Bilateral hippocampus volumes were calculated using the automated anatomical labeling (AAL) template.

Swept-source optical coherence tomography and swept-source optical coherence tomography angiography examination

SS-OCT/SS-OCTA (VG200S; SVision Imaging, Henan, China; version 2.1.016) was used to image the retinal structure and microvasculature of all participants. Retinal image acquisition was done in both eyes. Previous reports have detailed the specifications of the SS-OCT/OCTA tool (Kwapong et al., 2022a,b; Tao et al., 2022; Ye et al., 2022). Structural OCT imaging was done with 18 radial B-scans positioned on the fovea. Each B-scan was generated by 2048 A-scans, was 12 mm long, and separated from adjacent lines by 10 degrees. Each B-scan was automatically averaged 64 times to improve the signal-to-noise ratio (Alonso-Caneiro et al., 2011). Automatic segmentation of the retinal thickness was done by the OCT tool. Our current study focused on the macular retinal nerve fiber layer (mRNFL), and ganglion cell-inner plexiform layer (GCIPL) in a 3 × 3 mm^2 area around the fovea as shown in **Figure 1A**. The OCT tool provided the mean thicknesses (measured in μm) of the retinal structure.

The OCTA images covered an area of 3 × 3 mm^2 centered on the fovea. The *en face* angiograms of the superficial vascular complex (SVC) and deep vascular complex (DVC) were generated by the OCTA tool. The segmentation of the SVC and DVC slabs was set in the inner two-thirds and outer one-third border of GCIPL as shown in **Figure 1B**. Mean percentages (%) of the microvasculature in the SVC and DVC were obtained with an in-built algorithm in the OCTA tool.

All retinal measurements were done at the macula. OCT/OCTA data displayed in our study followed the OSCAR-IB quality criteria (Tewarie et al., 2012) and APOSTEL recommendation (Aytulun et al., 2021).

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), while skewed distribution was shown as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages (%). The z scores of all brain MRI volumes and cognitive measures were calculated. Multivariate linear regression based on a generalized estimating equation was used to investigate the association between SS-OCT/OCTA parameters, cognitive measures, and neuroimaging parameters while adjusting for gender, age, inter-eye dependencies, and vascular risk (hypertension, diabetes mellitus, hyperlipidemia, alcohol intake, and current smokers). We additionally adjusted for education years when the outcome was the cognitive measures and hippocampal volume. Multivariate regression was used to investigate the association between neuroimaging parameters and cognitive function while adjusting for risk factors and intracranial volume. All analyses were performed with R version 4.2.1 using R Studio and R Markdown (RStudio Inc., Boston, MA). *P*-values less than 0.05 ($P < 0.05$) were considered statistically significant. The Bonferroni method was used for the correction of multiple comparisons. We performed a *post-hoc* power calculation to evaluate the statistical power of GEE in our study; the statistical power of GEE in our study was $P < 0.001$.

Results

Figure 2 shows the flow chart of our data cohort. Two hundred and sixty-four eyes from 135 participants were included in our data analysis; 6 eyes were excluded because of poor imaging quality. The characteristics of the analyzed

1 http://dbm.neuro.uni-jena.de/cat/

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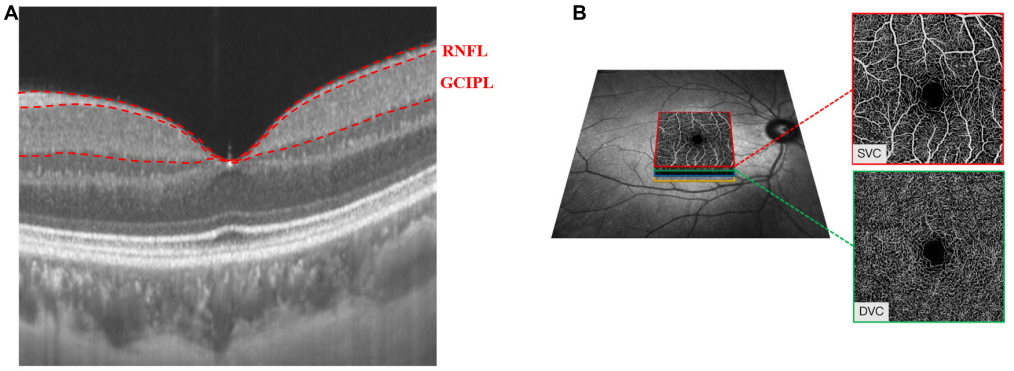

FIGURE 1
Retinal microvasculature and sub-layer thicknesses in a 3 mm × 3 mm area around the fovea. The radial scan model shows the RNFL and GCIPL thicknesses of the macula **(A)**. The SVC and DVC were set in the inner two-thirds and outer one-third border of GCIPL **(B)**.

data are shown in Table 1. The median age was 58 years (IQR 53–64 years) and the median years of education were 12. Out of the 135 participants, 91 (67.41%) were females and none had dementia; 24 had a history of hypertension while 21 (17.04%) were current smokers and 28 (20.74%) were current drinkers. The average SS-OCT/OCTA parameters were as follows: mRNFL thickness = 18.62 ± 1.77 μm, GCIPL thickness = 69.65 ± 7.04 μm, SVC density = 35.86 ± 5.14%, and DVC density = 46.36 ± 4.54% as shown in Table 1.

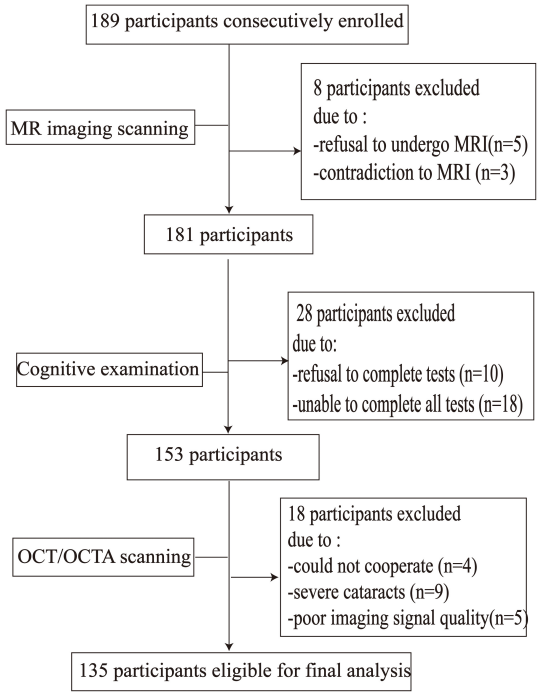

FIGURE 2
Flow chart diagram of the inclusion and exclusion criteria of our participants.

Figure 3 shows the correlation between OCT and OCTA parameters and the association between OCT/OCTA parameters and cognitive measures. Retinal thicknesses

TABLE 1 Characteristics of the study population.

Characteristics	*N*
Number	135
Age (years)	58 (53–64)
Gender (females)	91 (67.41%)
Education (years)	12 (9–16)
Hypertension (*n*)	24 (17.78%)
Diabetes (*n*)	4 (2.96%)
Dyslipidemia (*n*)	23 (17.04%)
Smokers (*n*)	21 (15.56%)
Drinkers (*n*)	28 (20.74%)
Cognitive function, raw scores	
MMSE	29 (28–30)
MoCA	26 (24–28)
Stroop A (s)	27 (22–31)
Stroop B (s)	41 (35–53)
Stroop C (s)	75 (63–96)
STT-A (s)	22 (16–36)
STT-B (s)	138 (111–192)
Total intracranial volume	1,360.71 (1,294.45–1,475.27)
Average hippocampal volume	3.98 (3.73–4.93)
GMV	602 (573.49–630.94)
WMV	484.06 (461.02–523.53)
SVC (%)	35.86 ± 5.14
DVC (%)	46.36 ± 4.54
RNFL (μm)	18.62 ± 1.77
GCIPL (μm)	69.65 ± 7.04

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; STT, Shape Trail Test; GMV, gray matter volume; WMV, white matter volume; SVC, superficial vascular complex; DVC, deep vascular complex; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer.

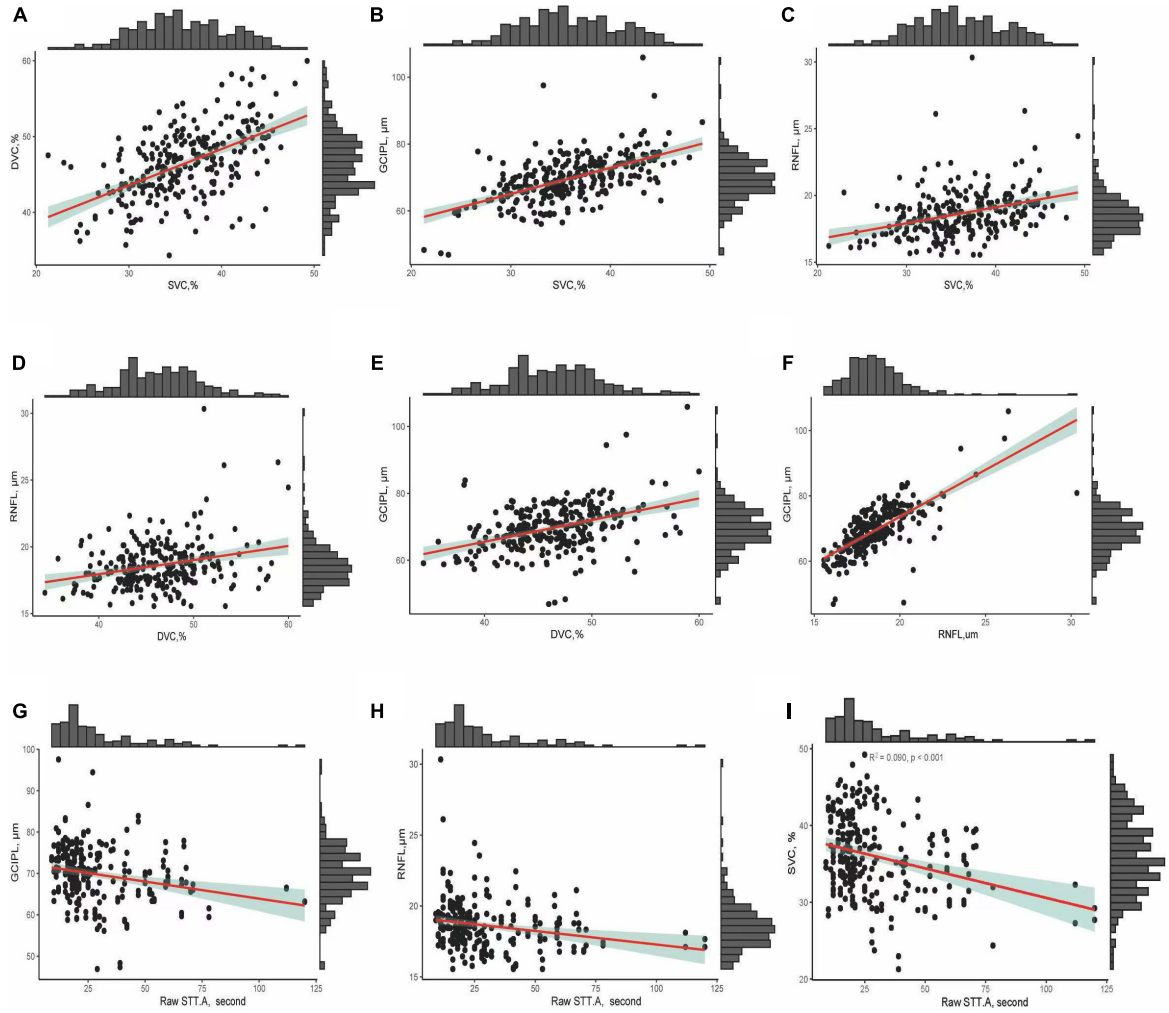

FIGURE 3
(A–F) Show the correlation between OCT/OCTA parameters. **(G–I)** Show the correlation between OCT/OCTA parameters and STT-A without adjusting for risk factors.

positively correlated with microvascular densities; importantly, STT-A correlated with mRNFL, GCIPL, and SVC (all $P < 0.001$).

Correlation between swept-source optical coherence tomography/optical coherence tomography angiography parameters and cognitive measures

Table 2 shows the correlation between OCT/OCTA parameters and cognitive measures after adjusting for risk factors. STT-A correlated with SVC ($P < 0.001$), DVC ($P = 0.015$) and mRNFL ($P = 0.013$) while STT-B correlated with SVC ($P = 0.020$) and GCIPL ($P = 0.015$). mRNFL thickness correlated with MoCA ($P = 0.007$) and Stroop A ($P = 0.030$). Importantly, SVC correlated with (STT B – STT A; $P < 0.001$, data not shown). DVC density ($P = 0.070$), mRNFL ($P = 0.696$), and GCIPL ($P = 0.846$) thicknesses did not show any significant correlation with the difference between STT B and STT A.

Correlation between swept-source optical coherence tomography/optical coherence tomography angiography parameters and neuroimaging parameters

After adjusting for risk factors and total intracranial volume, SVC correlated with average hippocampal volume ($P < 0.001$, Table 3).

Correlation between neuroimaging parameters and cognitive measures

We observed multiple correlations between cognitive measures and neuroimaging parameters as shown in Table 4; the average hippocampal volume correlated ($P < 0.05$) with most cognitive measures. Stroop B ($P < 0.001$) and Stroop C ($P = 0.020$) correlated with WMV while Stroop measures and STT-A correlated with GMV ($P < 0.05$).

TABLE 2 Correlation between SS-OCT/OCTA parameters and cognitive measures.

		MMSE	MoCA	Stroop A	Stroop B	Stroop C	STT-A	STT-B	STT B - STT A	RAVLT(IR)	RAVLTDR
SVC	B	0.193	0.088	−0.529	−0.922	−0.396	−1.700	1.016	1.251	0.603	−0.057
	SE	0.477	0.528	0.393	0.427	0.389	0.476	0.433	0.329	0.340	0.355
	P-value	0.686	0.867	0.180	0.031*	0.310	< 0.001*	0.020*	< 0.001*	0.077	0.872
DVC	B	−0.252	−0.162	−0.155	−0.688	0.181	−0.965	0.366	0.500	0.172	−0.129
	SE	0.390	0.432	0.323	0.350	0.319	0.394	0.358	0.274	0.280	0.290
	P-value	0.518	0.078	0.631	0.051	0.572	0.015*	0.307	0.070	0.539	0.657
RNFL	B	0.133	0.463	−0.346	−0.117	−0.102	−0.347	−0.101	−0.043	−0.043	−0.002
	SE	0.156	0.170	0.158	0.143	0.129	0.139	0.127	0.110	0.112	0.116
	P-value	0.393	0.007*	0.030*	0.413	0.429	0.013*	0.429	0.696	0.695	0.984
GCIPL	B	0.299	1.139	−0.242	−1.528	0.363	−0.98	0.320	0.084	−0.850	−0.690
	SE	0.616	0.678	0.566	0.622	0.510	0.553	0.504	0.434	0.438	0.456
	P-value	0.628	0.095	0.667	0.015*	0.476	0.078	0.525	0.846	0.054	0.132

P-values adjusted for age, gender, education, smoking, drinking, hypertension, diabetes, and dyslipidemia.
B, beta coefficient; SE, standard error; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; STT, Shape Trail Test; IR, immediate recall; DR, delayed recall; SVC, superficial vascular complex; DVC, deep vascular complex; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer.
*Significant difference ($P < 0.05$).

TABLE 3 Correlations between SS-OCT/OCTA parameters and brain MRI volume.

		Hippocampus[I]	WMV	GMV
SVC	B	−1.675	−0.013	−0.019
	SE	0.311	0.012	0.014
	P-value	< 0.001*	0.290	0.180
DVC	B	−0.33	−0.01	−0.022
	SE	0.283	0.01	0.126
	P-value	0.244	0.343	0.071
RNFL	B	−0.035	0.006	−0.005
	SE	0.107	0.004	0.004
	P-value	0.746	0.113	0.290
GCIPL	B	−0.059	0.019	−0.01
	SE	0.423	0.016	0.019
	P-value	0.889	0.237	0.612

P-values adjusted for age, gender, smoking, drinking, hypertension, diabetes, dyslipidemia, and total intracranial volume.
B, beta coefficient; SE, standard error; SVC, superficial vascular complex; DVC, deep vascular complex; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer, WMV, white matter volume; GMV, gray matter volume.
[I]*P*-values adjusted for age, gender, education, smoking, drinking, hypertension, diabetes, dyslipidemia, and total intracranial volume.
*Significant difference ($P < 0.05$).

Discussion

The present study showed that retinal thickness measured by OCT and retinal microvasculature measured by OCTA correlated with cognitive measures. After adjusting for risk factors and total intracranial volume, neuroimaging analysis showed hippocampal volume correlated with SVC density. Similar significant associations were also observed between cognitive measures and neuroimaging parameters. Our findings suggest that retinal thickness and microvasculature may reflect neuroimaging parameters associated with domains of cognition function and ensuing cognitive impairment in elderly adults.

STT is based on Trail Making Test and was developed for individuals who speak Chinese Mandarin as their first language. Population studies (Ko et al., 2018; Mutlu et al., 2018) have shown an association between thinner RNFL with worse cognitive performance (STT-A). We showed STT-A scores inversely correlated with SVC and DVC densities and RNFL thickness. STT-A assesses executive function, specifically attention and cognitive speed (Zhao Q. et al., 2013); these functions are frequently impaired in elderly adults and the aging population with cerebral disorders. OCTA reports have shown patients with dementia and other cerebral disorders have reduced SVC density and thinner RNFL and GCIPL thicknesses compared to controls (Kashani et al., 2021; Snyder et al., 2021). Thus, the associations between SS-OCT/OCTA parameters and STT examination give meaningful suggestions for retinal imaging research for cognitive assessment in elderly individuals. Noteworthy, we showed that SVC correlated with

TABLE 4 Correlation between cognitive measures and brain MRI volume.

	Hippocampus			WMV			GMV		
	B	SE	*P*-value	B	SE	*P*-value	B	SE	*P*-value
MMSE	0.209	0.093	0.026*	0.912	2.487	0.715	1.545	2.108	0.464
MoCA	0.28	0.101	0.006*	2.923	2.739	0.285	−4.435	2.293	0.054
Stroop A	0.329	0.074	< 0.001*	−0.239	2.035	0.906	5.552	1.682	0.001*
Stroop B	0.241	0.082	0.003*	−8.734	2.143	< 0.001*	5.425	1.84	0.003*
Stroop C	0.153	0.075	0.043*	−4.672	1.996	0.020*	4.926	1.676	0.004*
STT-A	0.614	0.086	< 0.001*	−0.713	2.512	0.777	8.236	2.057	0.001*
STT-B	−0.088	0.085	0.299	−1.231	2.248	0.585	2.209	1.896	0.245
RAVLT (IR)	−0.218	0.065	0.001*	−1.574	1.767	0.374	−1.163	1.493	0.437
RAVLT (DR)	−0.051	0.069	0.466	0.603	1.84	0.740	−0.308	1.559	0.843

P-values adjusted for age, gender, education, smoking, drinking, hypertension, diabetes, dyslipidemia, and total intracranial volume.
B, beta coefficient; SE, standard error; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; STT, Shape Trail Test; I C-RAVLT (IR), The Chinese Rey Auditory Verbal Learning Test (immediate recall); C-RAVLT (DR), The Chinese Rey Auditory Verbal Learning Test (delayed recall); GMV, gray matter volume; WMV, white matter volume.
*Significant difference ($P < 0.05$).

the difference in STT-B and STT-A, which removes the influence of speed.

Stroop is a cognitive tool that assesses the executive function of an individual, primarily focused attention; it helps in evaluating the behavioral control functions using the conflict between perception and speech (Zhao J. H. et al., 2013). Lee et al. suggested that poorer performances on Stroop B and Stroop C reflect genuine cognitive impairment. In our present study, we showed retinal thicknesses and retinal microvasculature had a significant correlation with Stroop parameters which is in line with previous reports (van Koolwijk et al., 2009; Mutlu et al., 2018). Our findings suggest that GCIPL thickness and SVC density may reflect cognitive dysfunction which is in line with previous reports (Jones-Odeh et al., 2016; Ko et al., 2018; Girbardt et al., 2021; Kim et al., 2022).

MoCA, as a general cognitive screening tool, correlated with RNFL thickness in our study. Previous reports (Oktem et al., 2015; Liu et al., 2019; Jeevakumar et al., 2022) have shown a significant correlation between OCT parameters and MoCA scores. Our findings suggest that thinner RNFL may indicate reduced MoCA scores which are in line with previous reports.

The pathophysiological elucidation for the association between SS-OCT/OCTA parameters and cognitive measures is interesting. Of note, these neuropsychological examinations require vision and the retina is the main processing visual medium in the central nervous system. Interpretation of these tests is accomplished in the retina where dementia reports have shown microvascular impairment and neurodegeneration (Snyder et al., 2021). Even though cognitive dysfunction may be related to cerebral damage, the involvement of the retina (both structural and microvessels) in cognition is supported by prior OCT/OCTA reports (Kashani et al., 2021; Snyder et al., 2021).

The underlying mechanism of SVC density and hippocampal volume is vague. It is postulated that retinal microvasculature reflects cerebral microcirculation. Animal reports (Koronyo et al., 2017; Shi et al., 2021) on dementia models showed deposition of amyloid-beta and tau in the retinal vessels and inner retinal structure, and autopsy reports (Blanks et al., 1989, 1996) on humans also showed these pathological changes in the retina. We showed a significant correlation between SVC density and hippocampal volume. Deposition of amyloid-beta, the pathological hallmark of dementia, has been reported to occur in the hippocampus and retina of mice simultaneously (Perez et al., 2009), suggesting that the development of dementia may involve neuron cell death of the brain (hippocampal atrophy) but also microvascular impairment of the retina. Similarly, hippocampal atrophy is a radiology indicator for Alzheimer's disease or dementia (Woodworth et al., 2022); recent reports suggest hippocampal atrophy may be due to vascular pathology, specifically small vessel disease and ischemia, which are implicated in the development of dementia (Kalaria, 2000; Iadecola, 2013). OCTA reports (Alber et al., 2020; Cheung et al., 2021) have shown reduced SVC density in patients with dementia compared to controls indicating ischemia. Given that hippocampal atrophy is a prominent feature of dementia, our findings that showed SVC density correlated with hippocampal volume suggests that microvascular impairment may lead to hippocampal atrophy.

It is suggested that the hippocampus plays a significant role in memory retrieval (St-Laurent et al., 2016; Ross et al., 2018); thus, hippocampal damage is linked with memory performance. We showed that hippocampal volume correlated with most cognitive measures and immediate recall memory. Our findings suggest that hippocampal volume is associated with cognitive measures and may contribute to recall memory particularly highlighting the role of cognitive speed and executive abilities in addition to information storage capacity (Friedman and Johnson, 2000). We also showed gray matter volume and white matter

volume correlated with cognitive measures which are in line with previous reports (Sasson et al., 2013; Ramanoel et al., 2018).

Investigation of the association between age-related changes in regional brain volumes and changes in cognitive measures may provide insights into the neural underpinnings of cognitive aging. Hippocampal volume, white matter, and gray matter volume correlated with cognitive tools which are reflective of executive function. Our findings highlight the clinical importance of volumetric analysis and its association with cognition in the aging population.

Mutlu et al. (2017) showed thinner peripapillary RNFL (pRNFL) thickness (thickness around the optic nerve head, ONH, which reflects the axonal integrity) was associated with smaller white matter volume and gray matter volume. Chua et al. (2021) did not show an association between mRNFL (retinal ganglion cell axon thickness at the macular) and white matter volume; the authors suggested that compared to the pRNFL, mRNFL is thinner and may not be sensitive to neurodegeneration. However, our current study did not show any significant association between retinal thickness at the macular and neuroimaging volumes. Further studies are needed to elucidate the association between retinal thickness and cerebral microstructural volumes.

There are some limitations in our study we would like to acknowledge. The observational, cross-sectional study design of our study is a major limitation, thus the association between SS-OCT/OCTA parameters, cognitive measures, and volumetric analysis of the brain should be interpreted with caution. Secondly, there was a possibility of a selection bias caused by the exclusion of individuals from our final data analysis; we excluded individuals with retinal abnormalities such as age-related macular degeneration (AMD), which are prevalent in aging individuals. This may have led to an underestimation of the observed correlations. Importantly, the participants enrolled in our study were Chinese which limits the generalizability of our findings. Thus, we suggest that the findings of our study should be corroborated by other races. Vision is needed for all neuropsychological examinations and the retina plays a significant role in visual processing; our study did not perform a visual acuity examination on our participants. The strengths of our study include the assessment of cerebral microstructural volume, retinal microvasculature, and structure. Both eyes were included in the analysis and GEE was used to account for the inter-eye correlation of an individual. Another strength of this study is the varying cognitive assessments performed in our study to reflect different cognitive domains. Thus, the association between these cognitive tools and retinal structure and microvasculature suggests that the retina may reflect cognition in elderly adults.

Our present study showed retinal thicknesses and microvasculature significantly correlated with cognitive measures and cerebral volumetric analysis in aging individuals. Our findings suggest that measurement of the retinal thickness and microvasculature by the SS-OCT/OCTA may be useful markers for assessing changes in cognitive function in elderly adults. Taken together, our study suggests that the retina (both structure and microvasculature) can be a pointer for cognitive performance, giving a choice for early discovery of decline in cognition and potential early treatment. Further studies with large sample sizes are required to validate the findings of this study.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of West China Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WK, RW, and WT: study concept, design, and data acquisition. RW, WK, LC, SZ, WT, JL, and CY: data analysis and interpretation. RW, JL, CY, WT, SZ, and WK: drafting of the manuscript. WK, RW, and SZ: critical review of manuscript. All authors approved of this version of the manuscript.

Funding

This study was funded by the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD18009), the National Natural Science Foundation of China (81870859, 92049115, 81671146, and 81870937), the National Key Research and Development Program of China of the Ministry of Science and Technology of China (2016YFC1300500-505 and 2018YFC1312300-303), and Post-Doctor Research Project, West China Hospital Sichuan University (2021HXBH081).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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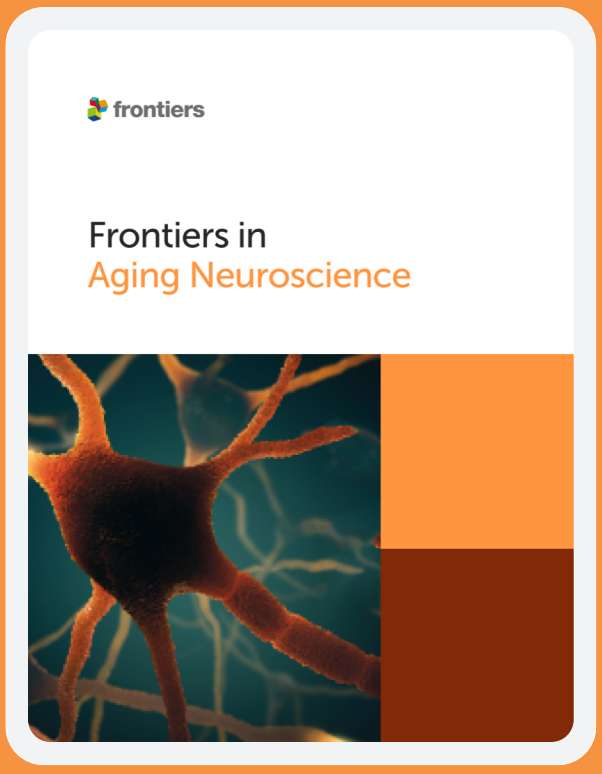

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